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temperature between the two gaseous substances A and B, calculated to be present at equilibrium in amounts of 10 and 90 per cent, respectively, a reduction of 3.1 kcal. per mole in the energy content of A would change the calculated equilibrium concentration of A from 10 per cent to over 95 per cent.

Present-day requirements for values of heats of formation place a heavy burden upon accuracy and precision in thermochemical measurements. Any given thermochemical investigation involves fundamentally, either directly or indirectly, the performance of two kinds of experiments. In one of these there is measured the amount of chemical reaction whose occurrence produces a specified change in the calorimeter, and in the other the quantity of electrical energy that produces the same change in the calorimeter (31). The chemical procedure and the calorimetric procedure are equally important in establishing the accuracy of the final thermochemical value.

The need for high accuracy is illustrated in the determination of the difference in the energy contents of the five isomers of hexane, which differences are of the order of 1 to 5 kcal. per mole. Since there is no simple chemical process susceptible of calorimetric measurement that involves the transformation of the various isomers, one into the other, one must select for measurement a series of five chemical reactions in which all the reactants and products are the same except the given isomer of hexane. When calorimetric observations are made on these chemical reactions under conditions which are substantially identical, the differences in the observed thermochemical values will be the differences in the heat or energy contents of the corresponding isomers of hexane. There is at present only one type of chemical reaction that can be used in this manner to determine the differences in the energy contents of the various isomers of hexane, and that is the reaction of combustion of the hydrocarbon in oxygen. Now the heat of combustion of normal hexane is about 1000 kcal. per mole, and the heats of combustion of the other isomers will differ from the value for normal hexane by only about 1 to 5 kcal. per mole. The determination of the difference in the energy contents of the various hexanes, therefore, depends significantly upon the chemical and calorimetric precision with which the heat of combustion of a given mass of the hydrocarbon can be determined. If the heat of combustion of each hexane can be determined with an estimated uncertainty of 1 part in 1000, or ±1.0 kcal. per mole, then the difference in the values for any two of the hexanes will have an estimated uncertainty of ±1.4 kcal. per mole (34). This uncertainty is too large to determine satisfactorily quantities of the order of 1 to 5 kcal. per mole. However, if the measurement of the heat of combustion can be made with an estimated uncertainty of only 2 parts in 10,000, then the difference in the energy contents of any two of the isomers can be determined with an estimated uncertainty of only ±0.3 kcal. per mole. This is substantially the limit of the accuracy obtainable with present-day thermochemical apparatus and technic (31).

There are a number of cases where the difference in the heats of formation of two hydrocarbons can be determined from calorimetric measurements of a simple chemical reaction in which one of the hydrocarbons is a reactant, the other is a product, and any other reactants or products are elemental substances. Examples of this procedure and type of reaction include the determination, by measurement of the heat of hydrogenation, of the difference in the heats of formation of (*a*) a monoölefin or diolefin hydrocarbon and the corresponding paraffin, (*b*) an aromatic or partially hydrogenated aromatic hydrocarbon and the corresponding naphthene (cycloparaffin) hydrocarbon, and (*c*) an acetylene hydrocarbon and the corresponding paraffin hydrocarbon.

When the hydrogenated product is the same for two different unsaturated hydrocarbons, either olefinic or aromatic, the difference in the heats of hydrogenation will give the difference in the heats of formation of the corresponding unsaturated hydrocarbons. In this way, one can determine the differences in the heats of formation of all those unsaturated hydrocarbons having the same number and skeletal arrangement of carbon atoms in the molecule, provided the reaction of hydrogenation is clear-cut and susceptible of calorimetric measurement.

In the determination of heats of combustion, the estimated uncertainty, in calories per mole, is roughly proportional to the number of carbon atoms per molecule of the given substance, whereas, in heats of hydrogenation, the estimated uncertainty is (all other things being equal) substantially proportional to the number of moles of hydrogen added to 1 mole of the unsaturated hydrocarbon. In actual values of energy, and in percentages of the total amount of energy measured per mole of the substance investigated, estimated uncertainties have been reported as given in table 1 for determinations of heats of combustion and heats of hydrogenation. For the representative examples given, which, for the heats of combustion, are taken from the work of Rossini and collaborators at the National Bureau of Standards and, for the heats of hydrogenation, from the work of Kistiakowsky and collaborators at Harvard University, the average estimated over-all uncertainty is $\pm 0.02_4$ per cent for the combustion experiments and ±0.20 per cent for the hydrogenation experiments. It is obvious that, notwithstanding the lower percentage uncertainty attainable in the combustion experiments, the hydrogenation experiments possess a decided advantage in the actual uncertainty in kilocalories per mole as one goes to the larger molecules. The hydrogenation method is therefore to be preferred, wherever possible, in determining the difference in the heats of formation of a given unsaturated hydrocarbon and the corresponding saturated hydrocarbon, as 1-butene and *n*-butane, in determining the difference in the energy contents of two unsaturated isomeric hydrocarbons yielding the same hydrocarbon on hydrogenation, as 1-butene and 2-butene, and in determining the difference in the heats of formation of any two unsaturated hydrocarbons yielding the same hydrocarbon on hydrogenation, as 1-butene and 1,3-butadiene. The difference in the energy contents or heats of formation of two unsaturated hydrocarbons that do not yield the same paraffin hydrocarbon on hydrogenation can not be determined from hydrogenation experiments alone, and recourse must be had to combustion experiments alone or to a combination of combustion experiments and hydrogenation experiments. For example, suppose it is desired to know the difference in the energy contents (or heats of formation) of 1-butene and "isobutene" (2-methylpropene). This quantity can be evaluated in two different ways: (*a*) as the difference in the heats of combustion of 1-butene and "isobutene"; or (*b*) as the sum of the difference in the heats of hydrogenation of 1-butene and "isobutene" with the corresponding difference in the heats of combustion of *n*-butane and isobutane. Both methods should, of course, yield the same value within their respective limits of uncertainty.

TABLE 1

Estimated uncertainties for determinations of heats of combustion and heats of hydrogenation

SUBSTANCE	ESTIMATED OVER-ALL UNCERTAINTY FROM COMBUSTION EXPERIMENTS		ESTIMATED OVER-ALL UNCERTAINTY FROM HYDROGENATION EXPERIMENTS	
	kcal. per mole	*percentage*	*kcal. per mole*	*percentage*
C_2H_4	±0.07	$\pm 0.02_1$	±0.06	±0.18
C_2H_6	±0.11	$\pm 0.02_8$		
C_3H_6	±0.15	$\pm 0.03_0$	±0.06	±0.20
C_3H_8	±0.12	$\pm 0.02_3$		
C_4H_8			±0.06	±0.20
C_4H_{10}	±0.14	$\pm 0.02_0$		
C_5H_{12}	±0.20	$\pm 0.02_4$		
C_7H_{14}			±0.06	±0.20

II. UNITS OF ENERGY

The actual unit of energy in calorimetric investigations today is the international joule, which is derived from the mean solar second and the international electrical watt. The international electrical watt is based upon standards of electromotive force and resistance maintained in terms of international volts and international ohms at the various national standardizing laboratories. Conversion to the artificial calorie may be made by means of the definition

$$1 \text{ calorie} = 4.1833 \text{ international joules}$$

The International Committee on Weights and Measures, through its Advisory Committee on Electricity, had planned that the various national standardizing laboratories in 1940 would begin to calibrate standard cells and resistances in terms of absolute instead of international units (1), but conditions abroad have made necessary a postponement of the plan. However, when international agreement is obtained on the best relation between the international and absolute electrical units, it is expected that the national standardizing laboratories will calibrate standard cells and resistances in terms of absolute volts and absolute ohms. At that time, the actual unit of energy in calorimetric measurements will become the absolute watt (electrical), which will be as nearly equal to 10^7 ergs per second as present-day measurements will permit. In order then to retain the same artificial calorie as is at present being used in thermochemical reports and writings, a new factor for conversion to the artificial calorie may be used. The definition of the artificial calorie will then become

$$1 \text{ calorie} = (4.1833)(1 + a) \text{ absolute joules}$$

where $(1 + a)$ will be the then best value for the number of absolute watts in 1 international watt. At the present time, the best relation between the international watt and the absolute watt appears to be that derived from measurements of the absolute ohm and absolute ampere recently made at the National Bureau of Standards at Washington (5, 6, 7, 42) and at the National Physical Laboratory at London (12, 40, 41). These determinations are in excellent accord with one another and yield the relation

$$1 \text{ international watt} = 1.00020 \pm 0.00005 \text{ absolute watts}$$

The results of preliminary measurements made of the relation between the international ampere and the absolute ampere at the Physikalisch-Technische Reichsanstalt at Berlin (1) lead to a value several parts in 10,000 greater than that given above. It is hoped that this difference will be resolved at an early date.

III. STANDARD REFERENCE STATES

Following the practice of Lewis and Randall (21), the standard reference temperature is taken as 25°C., and the standard reference states for individual substances are taken as follows: For a liquid or solid substance, the standard reference state is the actual pure liquid or solid at a pressure of 1 atm. at the given temperature; for a gaseous substance, the standard reference state is the gas in the hypothetical state of unit fugacity (1 atm.), where the heat content is the same as that of the real gas at zero pressure. In each case, the standard state is indicated by a superscript zero attached to the letter symbol indicating the thermodynamic property involved, here the heat content, H^0.

In the case of a solid substance that exists in two crystalline forms, it is necessary to specify that form that is to serve as the standard reference state for the given substance. In the case of carbon, some uncertainty formerly existed with regard to the possible forms of graphite, and, in one compilation (3), diamond was selected as the standard reference state for carbon. However, a recent investigation on the thermochemistry of carbon, carried on coöperatively by the National Bureau of Standards and the Coal Research Laboratory of the Carnegie Institute of Technology, has shown that the existence of more than one form of graphite is extremely improbable, and there is now every reason to use graphite as the standard reference state for carbon (8, 14, 35).

When values of the heats of formation at 25°C. are to be converted to the corresponding ones at 0°K., for use in connection with statistically calculated values of the free-energy function, $(F^0 - H_0^0)/T$, the following values may be used for $H_{298.16}^0 - H_0^0$, the heat content at 25°C. referred to 0°K., for graphite and hydrogen: C(c, graphite), 1053.8 ± 12.5 int. j. per mole or 251.9 ± 3.0 cal. per mole; H_2(g), 8466.6 ± 2.0 int. j. per mole or 2023.9 ± 0.5 cal. per mole (33).

IV. HEATS OF FORMATION OF WATER AND CARBON DIOXIDE

In calculating the heats of formation of hydrocarbons from carbon and hydrogen in their standard states, the values of the heats of combustion of the hydrocarbons are combined with values for the heats of formation of water and carbon dioxide from their elements in the standard states. In the case of the unsaturated hydrocarbons whose heats of hydrogenation have been measured, the heat of formation of the unsaturated hydrocarbon may be calculated by combining the heat of hydrogenation with the heat of formation of the paraffin hydrocarbon, determined as just mentioned.

In order that all such tabulations of heats of formation shall be self-consistent and the values comparable with one another, it is important that selected "standard" values for the heats of formation of water and carbon dioxide be used throughout. While actually not necessary except for calculating heats of reaction in which solid carbon or gaseous hydrogen, or both, are among the reactants or products, it is desirable that the "standard" values used for the heats of formation of water and carbon dioxide be ones measured with an accuracy at least as great as that of any other thermochemical quantity of similar magnitude. Reliable values of heats of formation are now available for both water and carbon dioxide.

For the heat of formation of water from gaseous hydrogen and oxygen at 25°C., the following value has been reported[2] (33):

$$H_2(g) + \frac{1}{2} O_2(g) = H_2O(liq); \Delta H^0_{298.16} = -285{,}795 \pm 40 \text{ int. j. per mole} = -68{,}318.1 \pm 9.6 \text{ cal. per mole}$$

For the heat of formation of carbon dioxide from solid carbon (graphite) and gaseous oxygen at 25°C., the following value has been reported (33, 35):

$$C(c, \text{graphite}) + O_2(g) = CO_2(g); \Delta H^0_{298.16} = -393{,}355 \pm 46 \text{ int. j. per mole} = -94{,}029.8 \pm 11.0 \text{ cal. per mole}$$

(The above values expressed in calories are carried to more figures than are significant, so that one may recover the original value expressed in international joules on reconversion to that unit by means of the factor 4.1833.)

V. EXISTING DATA ON GASEOUS HYDROCARBONS

For the gaseous hydrocarbons, the existing thermochemical data that have been obtained with modern calorimetric apparatus and technic, and with due regard for the accuracy of the chemical as well as the calorimetric procedure, are, with the exception of data on one compound, all from the thermochemical laboratories at Harvard University and the National Bureau of Standards. The data from the latter laboratory are all on heats of combustion and those from the former are all on heats of hydrogenation.

The present review is limited to those hydrocarbons containing eight or less carbon atoms per molecule, and to those determinations made within the past fifteen years. The previous review (32) includes references to all the earlier work on these compounds. References to data on hydrocarbons in the liquid state are also included here, since these may be converted to the gaseous state by combination with the appropriate heats of vaporization. Unfortunately, however, no heats of vaporization of hydrocarbons above pentane have heretofore been measured at or near 25°C., and values calculated for this temperature, either from calorimetric data at the normal boiling point or from existing data on the vapor pressure-temperature relations, introduce an additional uncertainty into the values so derived for the heats of formation in the gaseous state.

[2] The following symbols are used to designate the physical state of a substance: c = crystal; liq = liquid; g = gas.

For paraffin hydrocarbons in the gaseous state, measurements of the heat of combustion were made on the following: methane (26), ethane (27), propane (27), *n*-butane (27), isobutane (30), *n*-pentane (27), 2-methylbutane (19, 39), and tetramethylmethane (19). For paraffin hydrocarbons in the liquid state, measurements of the heat of combustion were made on the following: *n*-hexane (13), *n*-heptane (13), and *n*-octane (13, 2).

For olefin hydrocarbons in the gaseous state, measurements of the heat of combustion were made on ethylene (36) and propylene (36), and measurements of the heat of hydrogenation were made on the following: ethylene (15), propylene (16), 1-butene (16), *trans*-2-butene (16), *cis*-2-butene (16), "isobutene" (16), 1-heptene (17), 2-pentene (mixture of *cis* and *trans*) (17), 2-methyl-1-butene (17), 2-methyl-2-butene (17), 3-methyl-1-butene (9), 2,3-dimethyl-1-butene (17), 2,3-dimethyl-2-butene (17), 3,3-dimethyl-1-butene (9), 4,4-dimethyl-1-pentene (9), 2,4,4-trimethyl-2-pentene (9), 2,4,4-trimethyl-1-pentene (9), allene (18), 1,3-butadiene (18), 1,3-pentadiene (9), 1,4-pentadiene (18), 1,5-hexadiene (18), and 2,3-dimethyl-1,3-butadiene (30).

For unsaturated cyclic (including aromatic) hydrocarbons in the gaseous state, measurements of the heat of hydrogenation were made on the following: cyclopentene (9), cyclopentadiene (18), cyclohexene (17), 1,3-cyclohexadiene (18), cycloheptene (4), cycloheptadiene (4), cycloheptatriene (4), cycloöctene (4), benzene (18), *o*-xylene (9), ethylbenzene (9), and vinylbenzene (9).

For acetylene hydrocarbons in the gaseous state, data on the heat of hydrogenation were reported for acetylene (4), methylacetylene (4), and dimethylacetylene (4).

For naphthene or cycloparaffin hydrocarbons in the gaseous state, modern data on the heat of combustion have so far been obtained only for cyclopropane (20). For naphthene hydrocarbons in the liquid state, data on the heat of combustion have been reported for methylcyclopentane (22) and cyclohexane (22).

VI. TABULATED VALUES OF HEATS OF FORMATION

In table 2 are given values for the heats of formation, from solid carbon (graphite) and gaseous hydrogen, of a number of paraffin, olefin, and acetylene hydrocarbons in the gaseous state at 25°C. These values were calculated by combining the "standard" values of the heats of formation of water and carbon dioxide with the appropriate data on the heats of combustion and hydrogenation of the hydrocarbons in the gaseous state. The values for the eight paraffin hydrocarbons listed are dependent upon the data on heats of combustion. The values for ethylene and propylene are weighted means of values derived from the data on heats of combustion alone and from a combination of data on heats of hydrogenation and the values for the heats of formation of the corresponding paraffins. The values for all the other olefins and for the acetylenes are derived from a combination of the data on heats of hydrogenation with the values for the heats of formation of the corresponding paraffins.

TABLE 2

Heats of formation of gaseous hydrocarbons from solid carbon (graphite) and gaseous hydrogen at 25°C.

SUBSTANCE	FORMULA AND STATE	$\Delta Hf^{\circ}_{298.16}$	
		int. j. per mole	*cal. per mole**
Paraffins:			
Methane.................	CH_4(g)	−74,735 ± 310	−17,865 ± 74
Ethane..................	C_2H_6(g)	−84,465 ± 450	−20,191 ± 108
Propane.................	C_3H_8(g)	−103,535 ± 520	−24,750 ± 124
n-Butane................	C_4H_{10}(g)	−124,305 ± 640	−29,715 ± 153
Isobutane................	C_4H_{10}(g)	−131,145 ± 550	−31,350 ± 132
n-Pentane...............	C_5H_{12}(g)	−145,325 ± 890	−34,739 ± 213
2-Methylbutane..........	C_5H_{12}(g)	−153,405 ± 640	−36,671 ± 153
Tetramethylmethane.....	C_5H_{12}(g)	−164,865 ± 950	−39,410 ± 227
Monoölefins:			
Ethylene.................	C_2H_4(g)	52,526 ± 280	12,556 ± 67
Propylene................	C_3H_6(g)	20,732 ± 460	4,956 ± 110
1-Butene.................	C_4H_8(g)	1,602 ± 750	383 ± 180
cis-2-Butene............	C_4H_8(g)	−5,806 ± 750	−1,388 ± 180
trans-2-Butene..........	C_4H_8(g)	−9,781 ± 750	−2,338 ± 180
"Isobutene" (2-methylpropene)..............	C_4H_8(g)	−13,407 ± 690	−3,205 ± 165
1-Pentene................	C_5H_{10}(g)	−19,427 ± 1260	−4,644 ± 300
cis-2-Pentene............	C_5H_{10}(g)	−26,794 ± 1260	−6,405 ± 300
trans-2-Pentene..........	C_5H_{10}(g)	−30,756 ± 1260	−7,352 ± 300
2-Methyl-1-butene........	C_5H_{10}(g)	−35,240 ± 840	−8,424 ± 200
3-Methyl-1-butene........	C_5H_{10}(g)	−27,518 ± 750	−6,578 ± 180
2-Methyl-2-butene........	C_5H_{10}(g)	−41,812 ± 750	−9,995 ± 180
Diolefins:			
Allene..................	C_3H_4(g)	192,624 ± 1090	46,046 ± 260
1,3-Butadiene............	C_4H_6(g)	112,384 ± 1000	26,865 ± 240
1,3-Pentadiene...........	C_5H_8(g)	79,002 ± 1260	18,885 ± 300
1,4-Pentadiene...........	C_5H_8(g)	106,946 ± 1260	25,565 ± 300
Acetylenes:			
Acetylene................	C_2H_2(g)	226,852 ± 980	54,228 ± 235
Methylacetylene..........	C_3H_4(g)	185,358 ± 1000	44,309 ± 240
Dimethylacetylne........	C_4H_6(g)	147,340 ± 1490	35,221 ± 355

* See the text for a discussion of the unit of energy.

VII. DISCUSSION

The hydrocarbons for which values of heats of formation are given in table 2 include only those on which calorimetric measurements were made on the hydrocarbon in the gaseous state. Values for those hydrocarbons whose heats of combustion in the liquid state only have been measured are withheld until reliable values for their heats of vaporization at 25°C. become available.

The values listed in table 2 for the heats of formation of the gaseous paraffin hydrocarbons indicate, within the limits of uncertainty with which measurements can be made today, that (*a*) the energy increment per CH_2 group is not constant for the gaseous normal paraffins from methane to pentane, and (*b*) the energy content of isomers is not constant, being less for the branched-chain isomers than for the straight-chain ones, and, for the pentanes, least for the most highly branched isomer, tetramethylmethane (neopentane). The fact that the differences between *n*-butane and isobutane (1.64 ± 0.20 kcal. per mole) and between *n*-pentane and 2-methylbutane (1.93 ± 0.26 kcal. per mole) are identical within their respective limits of uncertainty might lead one to expect a similar decrease in the energy content of a paraffin hydrocarbon for each single branch anywhere along its chain of carbon atoms. Likewise, one might expect that a double or neopentyl branching on one carbon atom anywhere in the molecule would produce a decrease in energy content substantially identical with that observed for the isomerization of *n*-pentane into tetramethylmethane (4.67 ± 0.31 kcal. per mole). It was with the thought of checking these expectations that a thermochemical investigation of the five hexanes was undertaken at the National Bureau of Standards (38). While this investigation has not yet been completed, the preliminary calculations indicate that, within the limits of uncertainty with which the measurements have been made, the assumptions relating to the constancy of the decrease in energy content for all single branches and for all double branches on the same carbon atom are not true. It appears that data on certain hydrocarbons above the hexanes will be necessary before estimates, having limits of uncertainty comparable to those attached to the experimental values, can be made for all the paraffin hydrocarbons in the gaseous state.

The thermochemical data now being obtained at the National Bureau of Standards on the hexanes and several higher paraffin hydrocarbons (38) will make possible (*a*) the evaluation of the heats of formation of these hexanes and higher hydrocarbons, (*b*) the evaluation of the heats of formation of the corresponding olefins whose heats of hydrogenation have already been measured (4, 9, 17, 18), (*c*) an improvement in the accuracy of the extrapolation of the heats of formation of the gaseous normal paraffins beyond pentane and hexane (see reference 28), (*d*) a similar improvement in the accuracy of the extrapolation of the heats of formation of the gaseous normal olefins (1-alkenes) (see reference 37), (*e*) a reliable estimation of the heats of formation of all the remaining branched-chain paraffin hydrocarbons in the gaseous state that will not have been measured, and (*f*) a similar reliable estimation of the heats of formation of the remaining gaseous olefin hydrocarbons that will not have been measured.

In considering differences in the energy contents of isomeric hydrocarbons, and, in general, changes in the energy content corresponding to structural changes in hydrocarbons, it is desirable when possible to compare the appropriate values of the heats of formation for 0°K. rather than for 25°C., in order to eliminate the translational, rotational, and ordinary vibrational energy. For this purpose, there are required values of $H^0_{298.16} - H^0_0$, the heat content at 25°C. referred to 0°K., for solid carbon (graphite), gaseous hydrogen, and the gaseous hydrocarbons. Values for carbon and hydrogen have already been given (see page 6). Values for a number of the gaseous hydrocarbons have already been calculated (24) and others are being calculated (25). For the butanes and pentanes, the effect of the elimination of the rotational and ordinary vibrational energy is to reduce significantly the magnitude of the difference in the energy contents of two given isomers, as follows:

ISOMERIZATION	$\Delta H^0_{298.16}$	$\Delta H^0_{298.16} - \Delta H^0_0$	ΔH^0_0
	kcal. per mole	*kcal. per mole*	*kcal. per mole*
(*n*-butane) = (isobutane)......	−1.64 ± 0.20	−0.37 ± 0.07	−1.27 ± 0.21
(*n*-pentane) = (2-methylbutane)....................	−1.93 ± 0.26	−0.51 ± 0.07	−1.42 ± 0.27
(*n*-pentane) = (tetramethylmethane)....................	−4.67 ± 0.31	−0.63 ± 0.07	−4.04 ± 0.32

In table 3 are given values for the relative energy contents, at 0°K., of the isomers of butane and those of pentane, referred respectively to *n*-butane and *n*-pentane as zero. These values were derived from heats of combustion, with the corrections to 0°K. being made with the values of $H^0_{298.16} - H^0_0$ provided by Pitzer (25). At 0°K., then, where the molecules possess no translational, no rotational, and no ordinary vibrational energy, isobutane is more stable than *n*-butane by 1.27 ± 0.21 kcal. per mole. Likewise, 2-methylbutane is more stable than *n*-pentane by 1.42 ± 0.27 kcal. per mole, and tetramethylmethane is more stable than *n*-pentane by 4.04 ± 0.32 kcal. per mole.

Table 4 gives similar information for the butenes, with the values for *cis*-2-butene and *trans*-2-butene being derived from heats of hydrogenation and that for "isobutene" from a combination of heats of hydrogenation with heats of combustion. The corrections to 0°K. were made with values of $H^0_{298.16} - H^0_0$ provided by Pitzer (25). At 0°K., *cis*-2-butene is more stable than 1-butene by 1.84 ± 0.12 kcal. per mole, *trans*-2-butene by 2.79 ± 0.12 kcal. per mole, and "isobutene" by 3.85 ± 0.25 kcal. per mole.

TABLE 3

Energies of isomerization of the butanes and of the pentanes

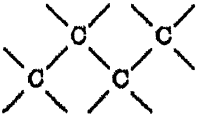
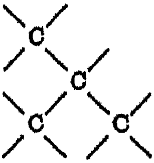
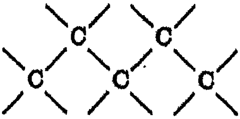
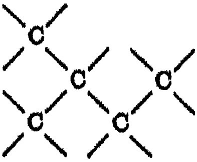
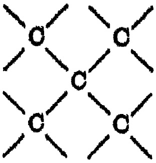
		RELATIVE ENERGY CONTENT AT 0°K.
		kcal. per mole
n-Butane.		0.00
Isobutane.		−1.27 ± 0.21
n-Pentane.		0.00
2-Methylbutane.		−1.42 ± 0.27
Tetramethylmethane.		−4.04 ± 0.32

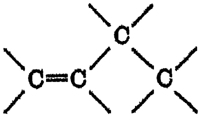
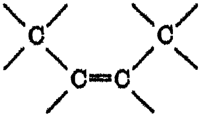
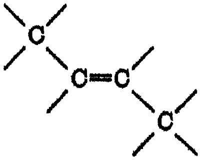
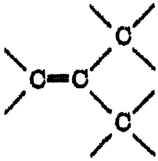
Table 5 gives similar information for four of the six pentenes (the values for *cis*-2-pentene and *trans*-2-pentene not being included because they were not measured separately). These values were derived from a combination of heats of hydrogenation and heats of combustion. At

25°C., with regard to energy content, 3-methyl-1-butene is more stable than 1-pentene by 1.93 ± 0.30 kcal. per mole, 2-methyl-1-butene by 3.78 ± 0.30 kcal. per mole, and 2-methyl-2-butene by 5.35 ± 0.30 kcal. per mole.

The energy of isomerization of 1,4-pentadiene into 1,3-pentadiene, as derived from heats of hydrogenation (see table 2), is $\Delta H^0_{298.16} = -6.68 \pm 0.25$ kcal. per mole. With regard to energy content, the 1,3-pentadiene is thus more stable by nearly 7 kcal. per mole.

TABLE 4

Energies of isomerization of the butenes

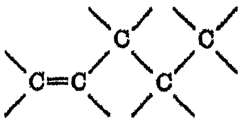
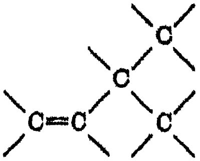
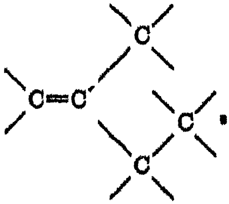
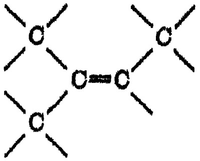
COMPOUND		RELATIVE ENERGY CONTENT AT 0°K.
		kcal. per mole
1-Butene.		0.00
cis-2-Butene.		−1.84 ± 0.12
trans-2-Butene.		−2.79 ± 0.12
"Isobutene" (2-methylpropene)...		−3.85 ± 0.25

While sufficient data are not yet available to make reliable quantitative estimates of the specific effects, the differences in the energy contents of isomers and the lack of constancy of the energy increment per CH_2 group may be ascribed to interactions between near neighbor atoms not directly bonded to one another. This interaction between non-bonded neighboring atoms was deduced from the data on the heats of combustion of paraffin hydrocarbons and normal alkyl primary alcohols (28, 29) and definitely confirmed by the data on heats of hydrogenation of olefin hydrocarbons, a complete discussion of which has recently appeared (4). Theoretical evaluations of the magnitude of such interactions have not yet been successfully made (10, 11).

Similar effects of interaction between non-bonded near-neighbor atoms have been found among the unsaturated cyclic hydrocarbons (4), although additional data are required before a complete interpretation can be made. This need for additional data is also true for the hydrocarbons of the aromatic and naphthene series. The aromatic ring nuclei involve consideration also of the "resonance" energy (23), and the naphthene ring nuclei of the departure of the bond angles from the normal tetrahedral value.

TABLE 5

Energies of isomerization of the pentenes

COMPOUND		RELATIVE ENERGY CONTENT AT 25°C.
		kcal. per mole
1-Pentene.		0.00
3-Methyl-1-butene.		−1.93 ± 0.30
2-Methyl-1-butene.		−3.78 ± 0.30
2-Methyl-2-butene.		−5.35 ± 0.30

On the basis of the data which are now available, it appears that the following factors impart greater stability to hydrocarbon molecules: (*a*) resonance, (*b*) minimum departure of the bond angles from the tetrahedral value, (*c*) maximum compactness of the carbon skeleton, and (*d*) minimum of repulsion between non-bonded atoms.

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THE PRESENT STATUS OF THE STATISTICAL METHOD OF CALCULATING THERMODYNAMIC FUNCTIONS[1]

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The formulas necessary for making approximate calculations of the entropy, free energy, heat content, and heat capacity of gases from a knowledge of their masses, moments of inertia, vibration frequencies, and internal hindrance potentials (if any) are given in a form ready for numerical calculation. Tables of vibrational contributions and energy levels for the internal libration problem are included. Higher-order effects are briefly discussed, as well as the question of securing the necessary data. Finally, an extensive bibliography of published calculations of the statistical type is appended, with a table by means of which the calculations dealing with any given molecule can readily be located.

The calculation of the thermodynamic properties of simple gases from a knowledge of the structure and vibration frequencies of their molecules is now a well-established and important method of obtaining data useful in engineering as well as scientific problems. Several descriptions (101, 42, 42a, 132a) of the principles and methods are available and a few reviews of applications have been published (101, 175, 176, 177, 178, 179). In this paper an effort will be made to describe advances in the theory made since the publication of the excellent review article by Kassel (101) and to tabulate the molecules which have been treated. In addition, a brief summary of the practical formulas will be given and some discussion of the methods of obtaining the required data. The appendices contain some useful tables.

I. SUMMARY OF PRACTICAL FORMULAS

As a practical proposition it is possible to consider the contributions of the electronic, vibrational, rotational, and translational energies separately, since they are very nearly additive. Refinements are considered later.

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[1] Presented at the Symposium on Fundamental Chemical Thermodynamics of Hydrocarbons and their Derivatives, which was held at the Ninety-ninth Meeting of the American Chemical Society, in Cincinnati, Ohio, April 10, 1940, under the auspices of the Division of Petroleum Chemistry of the American Chemical Society.

A. *Translational and rotational contributions*

The translational plus rotational contributions for non-linear rigid molecules are given by:

$$S^0 = 2.2875(3 \log M + 8 \log T - 2 \log \sigma + \log ABC) - 7.659 \qquad (1)$$

$$(F^0 - E_0^0)/T = -S + 7.948 \qquad (2)$$

$$H^0 - E_0^0 = 7.948\,T \qquad (3)$$

$$C_p^0 = 7.948 \qquad (4)$$

Here F^0, S^0, H^0, and C_p^0 are the translational and rotational contributions to the free energy, the entropy, the heat content (enthalpy), and the heat capacity at constant pressure for 1 mole of a perfect gas at 1 atm. pressure. The unit of energy is the calorie. E_0^0 is the energy per gram-mole of the perfect gas at the absolute zero. T is the absolute temperature, M the molecular weight, σ the symmetry number (see below), and A, B, C are the principal moments of inertia in units such that mass is given in atomic weight units and distance in Ångström units. The values of R etc. are those in the *International Critical Tables*.[2]

For linear (including diatomic molecules) the formulas are:

$$S^0 = 2.2875(3 \log M + 7 \log T - 2 \log \sigma + 2 \log I) - 6.632 \qquad (5)$$

$$(F^0 - E_0^0)/T = -S + 6.954 \qquad (6)$$

$$(H^0 - E_0^0) = 6.954T \qquad (7)$$

$$C_p^0 = 6.954 \qquad (8)$$

Here I is the moment of inertia in atomic weight-Ångström units.

The symmetry number σ is the number of indistinguishable positions into which the molecule can be turned by simple rigid rotations. For example, for hydrogen chloride, nitrogen, acetylene, ethylene, ammonia, and methane, σ is 1, 2, 2, 4, 3, and 12, respectively.

All the above are for the perfect gas at 1 atm. pressure. To correct for gas imperfection, see appendix I.

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[2] In the above equations, $2.2875 = 1/2\, R_1 \ln 10$, $7.948 = 4R_1$, $6.954 = (7/2)R_1$, $-7.659 = R_1 \ln (64\pi^5k^3R_2/h^6N^4 10^{24}) + 4R_1$, in which R_1 is the gas constant in calories, R_2 the gas constant in cc-atm., $\ln = \log_e$, and $\log = \log_{10}$.

It is important to note that the I. C. T. values of the physical quantities are not in accord with the best values more or less accepted to-day. Certain discrepancies have so far prevented general agreement, however, on a "best" set, so that the I. C. T. values are still used.

B. *Electronic contributions*

Let

$$Q = \sum_n g_n e^{-\frac{W_n}{kT}} \tag{9}$$

where W_n is an electronic energy level of degeneracy g_n, k is Boltzmann's constant, and the sum is over all electronic levels or in practice over all levels whose Boltzmann factors are not negligible. Then the electronic contributions are:

$$S = R \ln Q + RT \frac{\mathrm{d} \ln Q}{\mathrm{d}T} \tag{10}$$

$$(F/T) = -R \ln Q \tag{11}$$

$$(H/T) = RT \frac{\mathrm{d} \ln Q}{\mathrm{d}T} \tag{12}$$

$$C = RT^2 \frac{\mathrm{d}^2 \ln Q}{\mathrm{d}T^2} + 2RT \frac{\mathrm{d} \ln Q}{\mathrm{d}T} \tag{13}$$

Here ln is the natural logarithm, and R is the gas constant. Ordinarily only the lowest electronic level is of any importance and for that g_n is usually unity, so that in such cases all the above become zero.

C. *Vibrational contributions*

The formulas under "Electronic contributions" apply equally well to the vibrational contributions if the W_n are taken to be the vibrational levels. Usually it is necessary to assume that the vibrations are harmonic, in which case *each* fundamental frequency of vibration contributes the amounts below. It should be remembered that a non-linear molecule has $3N - 6$ frequencies, and a linear molecule $3N - 5$, where N is the number of atoms.

$$S = -R \ln (1 - e^{-w}) + R \frac{we^{-w}}{1 - e^{-w}} \tag{14}$$

$$(F/T) = R \ln (1 - e^{-w}) \tag{15}$$

$$H = RT \frac{we^{-w}}{1 - e^{-w}} \tag{16}$$

$$C = \frac{w^2 R}{2(\cosh w - 1)} \tag{17}$$

where

$$w = \frac{h\nu}{kT} = \frac{hc\omega}{kT} \tag{18}$$

in which ν is the frequency, ω the wave number, c the velocity of light, and h Planck's constant. Numerically:

$$w = 1.4324\,\frac{\omega}{T}; \quad w_{298.1} = 0.0048052\,\omega \tag{19}$$

Appendix II contains a complete table of the vibrational contributions to C, F/T, etc., as a function of ω/T. This table was obtained by interpolation from a smaller one computed by Dr. H. L. Johnston. I am deeply indebted to Dr. Johnston for permission to make use of this.

D. Nuclear spin and other effects

Except for hydrogen and at impractically low temperatures for other molecules, the question of nuclear spin, ortho and para species, spin weights, and quantum effects in the rotational contributions (101) can be completely ignored in practical calculations. The entropy thus obtained is called the virtual entropy. The "absolute" entropy is greater by $R \ln g_s$, where g_s is the nuclear spin weight, but the virtual entropy is the quantity used in practice. The existence of isotopes can also be ignored except when dealing with artificially enriched systems, particularly of deuterium, or for calculations of very high accuracy.

The centrifugal distortion (168) of the molecule, due to rotation, and the coupling of rotational and vibrational angular momenta (170) are ordinarily quite small corrections which can be applied if necessary. The change of moment of inertia with vibrational state is another correction which usually cannot be made because the data are insufficient.

Probably the most serious error in the above simplified formulas is due to the assumption of harmonic vibrational levels. The actual levels are not equally spaced but converge as the dissociation limit is approached. For diatomic molecules sufficient information is usually available to enable this effect to be taken into account, and the same is true for a very small number of polyatomic molecules. The mathematical methods (101) are well developed, but the data required are seldom available for polyatomic molecules. The accuracy which can be attained in these cases therefore becomes less at high temperatures.

Another vibrational effect is the occurrence of resonance. Sometimes a pair of vibrational levels near to one another will interact in such a way as to be displaced from the positions predicted by the simple theory used above. This will cause a small change in the vibrational contribution, which can be computed if the actual positions of the levels are known experimentally. An example is carbon dioxide. The phenomenon is well understood but requires empirical information at present in order to be corrected for.

For precise calculations all these effects should be, and are, considered, but for most polyatomic molecules it is necessary to be content with the approximate results.

E. Non-rigid molecules

If the molecule contains groups which can rotate or oscillate with large amplitudes about bonds in the molecule, as is the case in ethane, the problem becomes more complicated. If the force resisting the torsional motion is very large (as in a double bond) it is sufficient to treat this motion as a vibration, and if the motion is unrestricted ("free internal" rotation) it may be treated as a classical rotation by methods developed by Eidinoff and Aston (40) and by Kassel (106, 107, 108). In general, however, the forces are intermediate. Pitzer (140) has published easily applicable tables for use in these cases, but they are based on a theory which neglects some important effects and they are therefore not always very close approximations although unquestionably useful. Crawford (25) has recently given a reasonably rigorous treatment for a wide class of molecules: namely, those in which any number of symmetrical groups (such as methyl groups) are attached to a rigid framework. Examples are dimethyl ether, propylene, tetramethylmethane, methyl alcohol, etc. His equations may be summarized as follows:

The contributions of the oscillating groups are additive and replace a corresponding number of vibrational contributions. For each group the contributions are given by:

$$S = R[\ln G + (K/G)] \tag{20}$$

$$(F/T) = -R(\ln G + Y_0) \tag{21}$$

$$(H/T) = R[(K/G) - Y_0] \tag{22}$$

$$C = R[(J/G) - (K/G)^2] \tag{23}$$

in which

$$G = (\Omega^{1/2} G_R + G_V), \quad K = (\Omega^{1/2} K_R + K_V), \quad J = (\Omega^{1/2} J_R + J_V) \tag{24}$$

and

$$G_V = \sum_V \exp(-Y_r); \quad G_R = \sum \exp(-\Omega Y_r) \tag{25}$$

$$K_V = \sum_V Y_r \exp(-Y_r); \quad K_R = \sum_R \Omega Y_r \exp(-\Omega Y_r) \tag{26}$$

$$J_V = \sum Y_r^2 \exp(-Y_r); \quad J_R = \sum \Omega^2 Y_r^2 \exp(-\Omega Y_r) \tag{27}$$

In addition:

$$Y_r = (m^2 h^2 / 32\pi^2 D\Omega RT) a_r \tag{28}$$

$$\Omega = 1 - D[(\lambda_A^2/A) + (\lambda_B^2/B) + (\lambda_C^2/C)] \tag{29}$$

Here A, B, C are the principal moments of inertia of the whole molecule (including the attached groups), D is the moment of inertia about its axis of the symmetrical group under consideration, λ_A, λ_B, λ_C are the cosines of the angles between the group axis and the principal axes, m is the number of minima of depth V (calories) in the restricting potential of the group, while the a_r are the eigen-values of the equation below. R, D, A, B, C in equation 28 are in C.G.S. units.

$$\frac{d^2\psi}{dx^2} + (a_r + 2\theta \cos 2x)\psi = 0 \tag{30}$$

with

$$\theta = (8\pi^2 D\Omega / h^2 m^2) V \tag{31}$$

A table of a_r as a function of θ is given in appendix III. The sums over R and V have the following significance: The energy levels of the torsional motion are vibrational in character for low levels, rotational in character for higher levels. In carrying out the summations the levels are divided into these two classes, the lower or vibrational levels being denoted by V, the upper or rotational by R. The selection of the dividing line is of course somewhat arbitrary but is indicated by a line in the tables of a_r.

The symmetry number to be used in calculating the over-all rotational contributions is the symmetry number for the rigid molecule, e.g., $\sigma = 1$ for CH_3OH (COH bent). The symmetry of the rotating group is most easily taken into account by summing over only part of the levels a_r: namely, over a_n and b_n with n even of Ince's tables (85), provided that m is the symmetry number of the group. The table in appendix III contains only these levels.

If $\Omega \rightarrow 1$, these equations go over into those used by Pitzer, and his tables may then be used. If Ω is small it may be necessary to use the still higher approximations described by Crawford, which are more difficult to apply than the approximations of equations 20 to 23.

In all of these treatments it has been assumed that the restricting potential has the form

$$\tfrac{1}{2} V (1 - \cos m\alpha) \tag{32}$$

where α is the angle of the rotating group, m is the number of minima in the restricting potential, and V is the depth of these minima.

II. DISCUSSION OF DATA REQUIRED

The most difficult part of the calculation of thermodynamic properties is the collection and interpretation of the necessary data. The translational part of the partition function offers no difficulty, because all that is required is the molecular weight. The rotational part requires a knowledge of the principal moments of inertia. These have not been obtained directly from spectroscopic investigations except for diatomic molecules and a very few simple hydrides, such as water, hydrogen sulfide, ammonia, and methane. However, the structures of a fairly large number of molecules have now been investigated by the electron diffraction method (13), so that their moments of inertia can be computed with sufficient accuracy for this purpose. In other cases the only information available is the structural information given by organic chemistry and the interatomic distances in tables of covalent radii (139). This is usually sufficiently reliable.

Since it is only necessary to have the product ABC of the principal moments, it is useful to note that

$$ABC = \begin{vmatrix} I_{xx} & -I_{xy} & -I_{xz} \\ -I_{xy} & I_{yy} & -I_{yz} \\ -I_{xz} & -I_{yz} & I_{zz} \end{vmatrix} \tag{33}$$

in which

$$I_{xx} = \sum_i m_i(y_i^2 + z_i^2), \qquad I_{xy} = \sum_i m_i x_i y_i, \text{ etc.}$$

Here m_i is the mass of the i^{th} atom and x_i, y_i, z_i are its coördinates in any convenient system of Cartesian coördinates whose origin coincides with the center of gravity of the molecule.

If the molecule has an internal rotational or torsional degree of freedom, it is necessary to know something about the potential barrier restricting this rotation. At the present time there is no theoretical method of calculating this barrier and very little reliable empirical information upon which to base estimates. However, much work is being done in this field at the Pennsylvania State College, the University of California, Princeton University, Harvard University, and elsewhere. Up till now it has always been necessary to assume that the barrier has a simple cosine form with a suitable number of minima. Such a function has only one parameter, the height of the barrier, provided the number of minima is obvious from the symmetry of the molecule. This parameter must be obtained from a comparison with experimental data at some one temperature, for example, the entropy from third-law measurements or the heat capacity of the gas.

When it has been obtained, the properties at other temperatures can then be calculated. There is hope that spectroscopic studies may give the barrier height in some cases, such as that of methyl alcohol. Table 1 gives some values of barrier heights, although not all these figures are certain.

The vibrational frequencies

The problem of determining the vibration frequencies is ordinarily the most difficult step and therefore merits a separate discussion. The fundamental frequencies appear in the infrared spectrum and in the Raman spectrum of the substance. Neither spectrum ordinarily gives all the frequencies and frequently both together do not. Furthermore, these spectra usually include other lines that are not fundamentals. In addition, the lines observed carry no tags to tell whether they are fundamentals and if so whether they are singly, doubly or triply degenerate. (For example, the bending vibration of carbon dioxide is doubly degenerate, since it can occur in either of two planes at right angles, both motions having the same frequency.)

TABLE 1

Heights of potential barriers

SUBSTANCE	HEIGHT OF BARRIER	SUBSTANCE	HEIGHT OF BARRIER
	calories		*calories*
Ethane	2750	Methyl alcohol	~3000 (?)
Propane	~3300	Methylamine	~3000
Propylene	≈2100	Dimethylacetylene	<500
Neopentane	~4200	Acetone	~1000

In order to disentangle the observations a number of methods may be employed. In the Raman, the polarization should be measured. This sets apart the symmetrical vibrations. In the infrared, the contour of the rotational envelope is useful in sorting out the lines, but to observe it requires powerful equipment. If deuterium derivatives of the substance can be prepared and studied, the shifts caused by the heavier mass of deuterium often enable an interpretation to be made. The intensities of the lines are a property which ought to be of great service, but the theory is not very well developed. The temperature coefficient of intensity serves to eliminate difference bands. Comparisons with related molecules are very useful. Finally, the mathematical analysis of the vibrations of the molecule by means of the theory of small vibrations is almost essential for a complete and certain analysis, especially when there are frequencies which are not found in either spectrum and must therefore be calculated.

The mathematical calculation of vibration frequencies divides into two parts. It is first necessary to have a set of force constants for the bonds of the molecule, and then the actual calculation must be carried through. The second step may be laborious, but it is at least straightforward and will therefore be discussed first. The elementary mathematical methods (37) for the study of small vibration are very old, since quantum mechanics is not required. These methods are good enough for very simple molecules, but become almost impossibly laborious for molecules with even five or six atoms. In recent years many elaborations have been developed to simplify the calculations. Among the most important is the use of the symmetry of the molecule (146) to break the problem up into independent parts. In addition, a technique has recently been developed which replaces much of the algebra by the use of tabulated quantities (171). Furthermore, work done for simpler molecules can be carried over intact for larger molecules of which the simpler form parts. The operations which remain difficult are the evaluation of large determinants and the solution of high-order algebraic equations.

The choice of force constants cannot be treated so formally. It is often possible to use a smaller number of force constants than frequencies, treat them as adjustable parameters, and get a fairly good fit with the experimental data, a process which serves to check the assignment of the frequencies observed and perhaps to provide frequencies not observed. Often there are too many force constants for this and it is necessary to bring in the frequencies of the deuterium derivatives in order to get sufficient data to evaluate all the constants. The most promising attack, however, seems to be the possibility of carrying over force constants from one similar molecule to another. For example, the force constants for stretching and bending a C—H bond in a methyl group seem to remain fairly constant from one molecule to another. This systematic study of force constants is proceeding steadily at the present time and should produce some quite useful generalizations in the near future. It is at least possible that frequencies may eventually be calculated with sufficient accuracy for rough thermodynamic properties with no appeal to experiment. That stage is not yet here, however.

III. CONCLUSION

It is clear that the statistical method has progressed to a stage where simple rigid polyatomic molecules such as methane, ethylene, benzene, etc. can be treated with a practical degree of accuracy, provided that a careful study of the vibration frequencies has been made. Furthermore, simple molecules with one or two internal torsional degrees of freedom, such as ethane, propylene, dimethyl ether, etc., can also be dealt with, again assuming that a study of the vibrations has been carried out, and in addition if at least one experimental measurement of heat capacity, entropy, or free energy is available for use in determining the barrier height of the torsion.

The chief difficulties in handling molecules of the types which can now be computed are the determination of the vibration frequencies and the barrier heights, if any, the latter difficulty being insoluble until the former is settled. Experience has shown that we do not yet know enough about vibrations to guess at vibration frequencies by analogy with other molecules. Such guesses are likely to be too inaccurate to give a good barrier height, although, if only a very rough value of the thermodynamic quantities is helpful, estimated frequencies may suffice.

More complicated molecules, such as chain hydrocarbons, have not yet been solved by these methods, except very roughly, but there is hope that the classes of molecules which can be treated will continue to expand in the future as it has in the past.

APPENDIX I

Corrections for gas imperfection

If H, C_p, S, and F represent the heat content (enthalpy), heat capacity at constant pressure, entropy, and free energy for the real gas, and H^0, C^0, etc. the corresponding quantities for the ideal gas at the same temperature, then the following relations hold:

$$H = H^0 + \int_0^p \left[V - T\left(\frac{\partial V}{\partial T}\right)_p\right] dp$$

$$C_p = C_p^0 - T\int_0^p \left(\frac{\partial^2 V}{\partial T^2}\right)_p dp$$

$$S = S^0 - \int_0^p \left[\left(\frac{\partial V}{\partial T}\right)_p - \frac{R}{p}\right] dp - R \ln p$$

$$F = F^0 + \int_0^p [V - (RT/p)]\, dp + RT \ln p$$

in which V is the molar volume, R the gas constant per mole, T the absolute temperature, and p the pressure in atmospheres. The quantities $H^0 = E^0 + RT$, $C_p^0 = C_V^0 + \mathrm{R}$, S^0, and F^0 are given in the first part of the paper.

Evidently equation of state data, i.e., V, $\left(\frac{\partial V}{\partial T}\right)_p$, and $\left(\frac{\partial^2 V}{\partial T^2}\right)_p$ as functions of p, are required. In default of better information, Berthelot's equation with constants obtained from critical data has often been used.

TABLE 2

Harmonic oscillator contributions

(ω/T)	C	(H^0/T)	$-(F^0 - E_0^0)/T$	(ω/T)	C	(H^0/T)	$-(F^0 - E_0^0)/T$
0.10	1.9885	1.8480	4.0016	0.50	1.9041	1.3596	1.3324
0.11	1.9828	1.8345	3.8261	0.51	1.9009	1.3487	1.3056
0.12	1.9820	1.8210	3.6671	0.52	1.8975	1.3379	1.2796
0.13	1.9811	1.8076	3.5219	0.53	1.8942	1.3272	1.2542
0.14	1.9802	1.7943	3.3884	0.54	1.8907	1.3165	1.2295
0.15	1.9792	1.7810	3.2650	0.55	1.8872	1.3059	1.2054
0.16	1.9782	1.7679	3.1505	0.56	1.8836	1.2954	1.1820
0.17	1.9770	1.7547	3.0437	0.57	1.8801	1.2849	1.1592
0.18	1.9758	1.7417	2.9438	0.58	1.8764	1.2745	1.1369
0.19	1.9746	1.7287	2.8499	0.50	1.8728	1.2642	1.1151
0.20	1.9733	1.7158	2.7616	0.60	1.8690	1.2539	1.0940
0.21	1.9710	1.7030	2.6783	0.61	1.8652	1.2437	1.0734
0.22	1.9705	1.6902	2.5993	0.62	1.8613	1.2335	1.0533
0.23	1.9690	1.6775	2.5244	0.63	1.8573	1.2234	1.0336
0.24	1.9674	1.6640	2.4533	0.64	1.8534	1.2134	1.0144
0.25	1.9658	1.6523	2.3856	0.65	1.8493	1.2034	0.9956
0.26	1.9641	1.6398	2.3210	0.66	1.8453	1.1935	0.9773
0.27	1.9623	1.6274	2.2594	0.67	1.8411	1.1837	0.9595
0.28	1.9604	1.6150	2.2004	0.68	1.8370	1.1739	0.9420
0.29	1.9586	1.6027	2.1439	0.69	1.8328	1.1642	0.9249
0.30	1.9566	1.5905	2.0898	0.70	1.8285	1.1545	0.9082
0.31	1.9546	1.5783	2.0378	0.71	1.8241	1.1449	0.8919
.32	1.9525	1.5662	1.9879	0.72	1.8197	1.1354	0.8760
0.33	1.9504	1.5542	1.9399	0.73	1.8153	1.1259	0.8604
0.34	1.9482	1.5422	1.8937	0.74	1.8108	1.1165	0.8451
0.35	1.9458	1.5303	1.8492	0.75	1.8063	1.1071	0.8302
0.36	1.9435	1.5185	1.8062	0.76	1.8017	1.0978	0.8156
0.37	1.9411	1.5067	1.7648	0.77	1.7971	1.0886	0.8018
0.38	1.9386	1.4950	1.7248	0.78	1.7924	1.0794	0.7878
0.39	1.9361	1.4834	1.6861	0.79	1.7877	1.0704	0.7736
0.40	1.9335	1.4718	1.6487	0.80	1.7830	1.0613	0.7602
0.41	1.9309	1.4603	1.6125	0.81	1.7782	1.0523	0.7471
0.42	1.9281	1.4488	1.5774	0.82	1.7733	1.0434	0.7343
0.43	1.9253	1.4375	1.5435	0.83	1.7685	1.0345	0.7217
0.44	1.9224	1.4261	1.5105	0.84	1.7636	1.0257	0.7094
0.45	1.9195	1.4149	1.4786	0.85	1.7586	1.0169	0.6973
0.46	1.9166	1.4037	1.4476	0.86	1.7536	1.0082	0.6854
0.47	1.9135	1.3926	1.4176	0.87	1.7485	0.9996	0.6738
0.48	1.9105	1.3815	1.3884	0.88	1.7435	0.9910	0.6624
0.40	1.9074	1.3705	1.3600	0.89	1.7384	0.9825	0.6513

TABLE 2—*Continued*

(ω/T)	C	(H^0/T)	$-(F^0 - E_0^0)/T$	(ω/T)	C	(H^0/T)	$-(F^0 - E_0^0)/T$
0.90	1.7332	0.9740	0.6403	1.30	1.5001	0.6804	0.3354
0.91	1.7279	0.9656	0.6296	1.31	1.4937	0.6741	0.3302
0.92	1.7227	0.9573	0.6191	1.32	1.4874	0.6679	0.3252
0.93	1.7174	0.9490	0.6088	1.33	1.4810	0.6618	0.3202
0.94	1.7121	0.9407	0.5987	1.34	1.4747	0.6556	0.3152
0.95	1.7067	0.9326	0.5887	1.35	1.4683	0.6495	0.3104
0.96	1.7013	0.9244	0.5790	1.36	1.4619	0.6435	0.3056
0.97	1.6958	0.9164	0.5695	1.37	1.4555	0.6375	0.3009
0.98	1.6905	0.9084	0.5601	1.38	1.4491	0.6316	0.2963
0.99	1.6849	0.9004	0.5509	1.39	1.4426	0.6257	0.2918
1.00	1.6794	0.8925	0.5419	1.40	1.4362	0.6198	0.2873
1.01	1.6738	0.8847	0.5331	1.41	1.4297	0.6140	0.2829
1.02	1.6682	0.8769	0.5244	1.42	1.4233	0.6082	0.2786
1.03	1.6626	0.8692	0.5159	1.43	1.4168	0.6025	0.2743
1.04	1.6569	0.8615	0.5076	1.44	1.4104	0.5968	0.2701
1.05	1.6512	0.8539	0.4994	1.45	1.4038	0.5912	0.2660
1.06	1.6454	0.8463	0.4913	1.46	1.3973	0.5856	0.2619
1.07	1.6397	0.8388	0.4834	1.47	1.3908	0.5801	0.2580
1.08	1.6339	0.8314	0.4756	1.48	1.3843	0.5746	0.2541
1.09	1.6281	0.8240	0.4680	1.49	1.3777	0.5691	0.2502
1.10	1.6223	0.8166	0.4605	1.50	1.3712	0.5637	0.2464
1.11	1.6164	0.8093	0.4532	1.51	1.3646	0.5583	0.2427
1.12	1.6105	0.8021	0.4459	1.52	1.3580	0.5530	0.2390
1.13	1.6045	0.7949	0.4389	1.53	1.3515	0.5478	0.2354
1.14	1.5986	0.7878	0.4319	1.54	1.3449	0.5425	0.2319
1.15	1.5926	0.7807	0.4250	1.55	1.3383	0.5373	0.2284
1.16	1.5866	0.7736	0.4183	1.56	1.3317	0.5321	0.2249
1.17	1.5805	0.7667	0.4117	1.57	1.3251	0.5271	0.2215
1.18	1.5745	0.7597	0.4052	1.58	1.3186	0.5220	0.2182
1.19	1.5684	0.7528	0.3988	1.59	1.3120	0.5170	0.2150
1.20	1.5623	0.7460	0.3925	1.60	1.3054	0.5120	0.2117
1.21	1.5562	0.7392	0.3863	1.61	1.2988	0.5071	0.2086
1.22	1.5500	0.7325	0.3803	1.62	1.2922	0.5021	0.2054
1.23	1.5438	0.7258	0.3743	1.63	1.2857	0.4974	0.2024
1.24	1.5376	0.7192	0.3685	1.64	1.2791	0.4925	0.1993
1.25	1.5314	0.7126	0.3627	1.65	1.2725	0.4878	0.1964
1.26	1.5251	0.7060	0.3571	1.66	1.2659	0.4830	0.1934
1.27	1.5189	0.6996	0.3515	1.67	1.2593	0.4784	0.1905
1.28	1.5126	0.6931	0.3460	1.68	1.2528	0.4737	0.1877
1.29	1.5064	0.6867	0.3407	1.69	1.2462	0.4691	0.1849

TABLE 2—*Continued*

(ω/T)	C	(H^0/T)	$-(F - E_0^0)/T$	(ω/T)	C	(H^0/T)	$-(F^0 - E_0^0)/T$
1.70	1.2396	0.4645	0.1821	2.20	0.9217	0.2799	0.08690
1.71	1.2330	0.4600	0.1794	2.22	0.9097	0.2741	0.08441
1.72	1.2265	0.4555	0.1768	2.24	0.8977	0.2684	0.08197
1.73	1.2298	0.4510	0.1741	2.26	0.8859	0.2629	0.07961
1.74	1.2133	0.4466	0.1716	2.28	0.8742	0.2575	0.07731
1.75	1.2067	0.4422	0.1690	2.30	0.8625	0.2521	0.07508
1.76	1.2001	0.4379	0.1665	2.32	0.8509	0.2469	0.07293
1.77	1.1936	0.4335	0.1640	2.34	0.8394	0.2417	0.07084
1.78	1.1872	0.4293	0.1616	2.36	0.8280	0.2367	0.06880
1.79	1.1806	0.4250	0.1592	2.38	0.8167	0.2317	0.06683
1.80	1.1740	0.4208	0.1568	2.40	0.8055	0.2268	0.06490
1.81	1.1675	0.4166	0.1545	2.42	0.7944	0.2220	0.06304
1.82	1.1609	0.4125	0.1522	2.44	0.7834	0.2173	0.06123
1.83	1.1544	0.4084	0.1500	2.46	0.7724	0.2127	0.05948
1.84	1.1479	0.4044	0.1477	2.48	0.7615	0.2082	0.05777
1.85	1.1414	0.4003	0.1456	2.50	0.7508	0.2038	0.05611
1.86	1.1349	0.3963	0.1434	2.52	0.7401	0.1995	0.05451
1.87	1.1284	0.3924	0.1413	2.54	0.7295	0.1953	0.05296
1.88	1.1219	0.3885	0.1392	2.56	0.7190	0.1911	0.05144
1.89	1.1155	0.3846	0.1371	2.58	0.7086	0.1870	0.04997
1.90	1.1090	0.3807	0.1351	2.60	0.6983	0.1830	0.04853
1.91	1.1025	0.3769	0.1331	2.62	0.6881	0.1791	0.04715
1.92	1.0961	0.3731	0.1312	2.64	0.6780	0.1752	0.04580
1.93	1.0897	0.3694	0.1293	2.66	0.6680	0.1714	0.04450
1.94	1.0833	0.3656	0.1274	2.68	0.6581	0.1677	0.04323
1.95	1.0768	0.3620	0.1255	2.70	0.6483	0.1641	0.04199
1.96	1.0705	0.3583	0.1237	2.72	0.6386	0.1606	0.04080
1.97	1.0642	0.3547	0.1219	2.74	0.6290	0.1571	0.03964
1.98	1.0578	0.3511	0.1201	2.76	0.6194	0.1537	0.03850
1.99	1.0514	0.3475	0.1183	2.78	0.6100	0.1504	0.03740
2.00	1.0451	0.3440	0.1166	2.80	0.6007	0.1471	0.03633
2.02	1.0325	0.3371	0.1132	2.82	0.5915	0.1439	0.03530
2.04	1.0199	0.3303	0.1099	2.84	0.5824	0.1408	0.03429
2.06	1.0074	0.3236	0.1067	2.86	0.5733	0.1377	0.03332
2.08	0.9950	0.3170	0.1036	2.88	0.5644	0.1347	0.03237
2.10	0.9826	0.3105	0.1006	2.90	0.5556	0.1317	0.03144
2.12	0.9703	0.3042	0.09771	2.92	0.5469	0.1288	0.03056
2.14	0.9580	0.2979	0.09489	2.94	0.5383	0.1260	0.02969
2.16	0.9459	0.2918	0.09215	2.96	0.5298	0.1232	0.02885
2.18	0.9338	0.2858	0.08949	2.98	0.5214	0.1205	0.02802

TABLE 2—*Concluded*

(ω/T)	C	(H^0/T)	$-(F^0-E_0^0)/T$
3.00	0.5131	0.1178	0.02722
3.05	0.4927	0.1114	0.02533
3.10	0.4730	0.1053	0.02356
3.15	0.4538	0.0995	0.02193
3.20	0.4353	0.0940	0.02041
3.25	0.4174	0.0888	0.01899
3.30	0.4001	0.0839	0.01767
3.35	0.3833	0.0792	0.01644
3.40	0.3672	0.0748	0.01530
3.45	0.3515	0.0707	0.01423
3.50	0.3365	0.0667	0.01325
3.55	0.3219	0.0630	0.01233
3.60	0.3079	0.0594	0.01148
3.65	0.2944	0.0560	0.01068
3.70	0.2814	0.0528	0.00994
3.75	0.2689	0.0498	0.00925
3.80	0.2569	0.0470	0.00861
3.85	0.2453	0.0443	0.00801
3.90	0.2342	0.0418	0.00746
3.95	0.2235	0.0394	0.00694
4.00	0.2133	0.0371	0.00646
4.1	0.1940	0.0330	0.00560
4.2	0.1763	0.0292	0.00485
4.3	0.1600	0.0259	0.00420
4.4	0.1451	0.0230	0.00364
4.5	0.1314	0.0204	0.00315
4.6	0.1190	0.0180	0.00273
4.7	0.1076	0.0160	0.00237
4.8	0.0972	0.0141	0.00205
4.9	0.0877	0.0125	0.00178
5.0	0.0792	0.01104	0.00154
5.1	0.0713	0.00976	0.001335
5.2	0.0643	0.00862	0.001157
5.3	0.0578	0.00762	0.001002
5.4	0.0520	0.00672	0.000869
5.5	0.0468	0.00593	0.000753
5.6	0.0420	0.00524	0.000652
5.7	0.0377	0.00462	0.000565
5.8	0.0339	0.00407	0.000490
5.9	0.0303	0.00359	0.000425
6.0	0.0272	0.00316	0.000367
6.1	0.0243	0.00279	0.000318
6.2	0.0218	0.00245	0.000276
6.3	0.0195	0.00216	0.000239
6.4	0.0174	0.00190	0.000207
6.5	0.0156	0.00167	0.000180
6.6	0.0139	0.00147	0.000156
6.7	0.0124	0.00130	0.000135
6.8	0.0111	0.00114	0.000117
6.9	0.00990	0.001002	0.0001013
7.0	0.00883	0.000880	0.0000877
7.1	0.00787	0.000774	0.0000760
7.2	0.00701	0.000680	0.0000659
7.3	0.00625	0.000597	0.0000571
7.4	0.00556	0.000525	0.0000495
7.5	0.00495	0.000461	0.0000429
7.6	0.00441	0.0004048	0.0000371
7.7	0.00392	0.0003553	0.0000322
7.8	0.00346	0.0003119	0.0000279
7.9	0.00310	0.0002738	0.0000242
8.0	0.00275	0.0002402	0.0000210
8.1	0.00245	0.0002108	0.0000182
8.2	0.00217	0.0001849	0.0000157
8.3	0.00193	0.0001622	0.0000136
8.4	0.00171	0.0001422	0.0000118
8.5	0.00152	0.0001247	0.0000102
8.6	0.00135	0.0001093	0.0000089
8.7	0.00119	0.0000958	0.0000077
8.8	0.00106	0.0000840	0.0000067
8.9	0.000939	0.0000736	0.0000058
9.0	0.000832	0.0000645	0.0000050
9.1	0.000737	0.0000565	0.0000043
9.2	0.000653	0.0000495	0.0000037
9.3	0.000578	0.0000434	0.0000032
9.4	0.000512	0.0000380	0.0000028
9.5	0.000454	0.0000332	0.0000024
9.6	0.000401	0.0000291	0.0000021
9.7	0.000354	0.0000255	0.0000018
9.8	0.000314	0.0000223	0.0000016
9.9	0.000277	0.0000196	0.0000014
10.0	0.000245	0.0000171	0.0000012

APPENDIX II

Harmonic oscillator contributions

The contribution (in calories) of a fundamental vibration frequency ω (wave numbers) to the heat capacity, heat content, and free energy are

TABLE 3

Values of a_r for various values of θ and r

$\theta = 0$	1	2	3	4	5	6
0.0000	−0.4551	−1.5140	−2.8344	−4.2805	−5.8000	−7.3688
4.0000	3.9170	3.6722	3.2769	2.7469	2.0995	1.3518
4.0000	4.3713	5.1727	6.0452	6.8291	7.4491	7.8701
16.000	16.033	16.128	16.273	16.452	16.648	16.845
16.000	16.034	16.141	16.339	16.650	17.097	17.689
36.000	36.014	36.057	36.129	36.229	36.359	36.517
36.000	36.014	36.057	36.129	36.230	36.361	36.523

$\theta = 7$	8	9	10	12	14	16
−8.9737	−10.607	−12.262	−13.937	−17.332	−20.776	−24.259
0.5175	−0.3894	−1.3588	−2.3822	−4.5635	−6.8907	−9.3341
8.0866	8.1152	7.9828	7.7174	6.8787	5.7363	4.3712
17.027	17.183	17.303	17.381	17.395	17.207	16.819
18.417	19.253	20.161	21.105	22.972	24.651	26.009
36.704	36.917	37.157	37.420	38.006	38.648	39.315
36.715	36.94	37.21	37.51	38.24	39.16	40.22

$\theta = 18$	20	24	28	32	36	40
−27.773	−31.313	−38.459	−45.673	−52.942	−60.256	−67.606
−11.873	−14.491	−19.923	−25.562	−31.365	−37.303	−43.352
2.8331	1.1543	−2.5398	−6.5881	−10.914	−15.467	−20.208
16.242	15.494	13.553	11.121	8.2947	5.1467	1.7300
26.988	27.595	27.885	27.283	26.062	24.379	22.325
39.972	40.590	41.606	42.225	42.394	42.118	41.433
40.93	42.1					

given in table 2 as a function of (ω/T). The contribution to the entropy is given by $S = (H/T) - (F/T)$. All constants are from the *International Critical Tables.* This table was obtained by interpolation from unpublished calculations of Dr. H. L. Johnston, to whom I should like to express my gratitude. The last decimal place may be in error by several units, owing to the interpolation.

TABLE 4

References for published calculations of thermodynamic quantities

SUBSTANCES	REFERENCES	SUBSTANCES	REFERENCES
Diatomic molecules			
Air	(99, 100)	HF	(136)
Br_2	(135, 150, 14, 78, 154, 166)	HI	(135, 134, 62)
C_2	(74)	I_2	(135, 134, 150, 63, 47)
D_2	(20, 100, 135, 166, 92)	ICl	(130)
DBr	(135)	Li_2	(71)
DCl	(135, 166a)	K_2	(71)
DI	(135, 166a)	Na_2	(71, 52, 89, 154, 166)
Cl_2	(135, 56, 150, 100, 165, 55, 166)	N_2	(149, 135, 100, 165)
CO	(149, 135, 100, 18, 19, 105, 89, 154, 166)	NO	(179, 149, 100, 91, 87, 172, 52)
F_2	(45, 136)	O_2	(149, 135, 100, 165, 94, 95, 154, 120, 122, 97, 166)
H_2	(100, 149, 135, 10, 36, 46, 76, 35, 154)	OH	(100, 90)
HBr	(135)	P_2	(66)
HCl	(135, 100, 55, 60, 154, 166)	S_2	(7, 65, 133, 34)
HD	(100, 135, 166, 92)	SO	(133)
Other inorganic substances			
$AsCl_3$	(173)	COS	(114, 7, 33, 100)
AsF_3	(173)	CS_2	(15, 7, 33, 100)
$B_3N_3H_6$	(28)	Cl	(55)
CBr_4	(160)	ClO_2	(166)
CCl_4	(127, 160, 173, 100)	Cu vapor	(112)
CF_4	(173, 100)	D	(92, 93)
CF_2Cl_2	(100)	D_2O	(98, 149, 125)
C_2N_2	(100, 17, 161, 147, 159)	HDO	(163, 30, 31, 32)
CNBr	(159)	D_2S	(98)
CNCl	(159)	Fe vapor	(112)
CNI	(159)	H	(46)
CO_2	(76, 67, 103, 166, 53, 149, 135, 100)	HCN	(8, 16, 73, 100, 57)
$COCl_2$	(160)	H_2S	(34, 23, 135, 7, 21, 100, 98)
		HDS	(98)

TABLE 4—*Concluded*

SUBSTANCES		SUBSTANCES	REFERENCES
Other inorganic substances—*Continued*			
H_2O	(50, 164, 76, 67, 68, 69, 154, 121, 166, 100, 98, 149, 135, 59, 49, 110, 48, 156)	P	(2)
		P_4	(11, 2)
		PBr_3	(173)
		PCl_3	(2, 173)
		PCl_5	(2)
		PF_3	(173)
I	(134)	PH_3	(22, 155, 100)
NH_3	(157, 51, 128, 16, 138, 149, 100, 80)	S	(133)
		SF_6	(100)
		$SiCl_4$	(81, 173)
N_2H_4	(41)	SiF_4	(173)
N_2O	(103, 12, 8, 145, 12, 100)	SO_2	(70, 166, 135, 7, 33)
NO_2	(179, 54)	$SnCl_4$	(81)
NOCl	(86, 9)	TeF_6	(100)
$Ni(CO)_4$	(27)	$TiCl_4$	(81)
O	(95, 96)	Xe	(24)
OsO_4	(1)	Electron gas	(72)
O_3	(104, 121)		
Organic compounds			
CH_4	(43, 100, 149, 131, 106, 102, 167, 158)	Allene	(124)
		Propylene	(141, 143, 100, 26, 107, 116)
CH_3D, etc.	(131)	Cyclopropane	(123)
CH_3Br	(160, 39)	Propane	(141, 107, 106, 113, 100, 116)
CH_3Cl	(160, 100, 167)		
CH_3NH_2	(6)	Isopropyl alcohol	(152)
CH_3OH	(108, 79)	Butane	(141, 106, 100)
CH_2Br_2	(160)	Isobutane	(141, 100, 106)
CH_2Cl_2	(160, 100, 167)	1-Butene	(141, 107, 100)
$CHBr_3$	(160)	2-Butene	(141, 107, 100)
$CHCl_3$	(160, 100, 167)	"Isobutene"	(141, 107, 100)
CH_2O	(160)	Butadiene	(107)
CHOOH	(160)	Dimethylacetylene	(29, 137)
		Neopentane	(4, 141, 106, 100)
C_2H_2	(100, 75, 102)		
C_2HD, C_2D_2	(75, 64)	$(CH_3)_2C{=}CHCH_3$	(107)
C_2H_4	(141, 38, 107, 162, 100, 102, 153)	C_6H_6	(100, 126, 106)
		C_6D_6	(126, 106)
C_2H_6	(115, 141, 162, 106, 117, 148, 100, 169, 153)	$(CH_3)_2C{=}C(CH_3)_2$	(107)
		Phenol	(3)
		Cresol	(3)
C_2H_5OH	(151)	Methyl derivatives of benzene	(106)
$(CH_3)_2CO$	(152)		
$(CH_3)_2NH$	(5)	Chain hydrocarbons	(83)

APPENDIX III

Energy levels for the torsional oscillator

Values of a_r for various values of θ and r are given in table 3. Only levels of symmetry A are included. The first six levels are taken from Ince (85). Levels higher than those given may be computed approximately by the asymptotic formula:

$$a_r = r^2 + \frac{1}{2}\,\theta/(r^2 - 1)$$

A line indicates the proper place to change from V to R levels.

APPENDIX IV

Tabulation of references of published calculations of thermodynamic quantities

Table 4 contains reference numbers for essentially all calculations which have been published up to 1940. References up to 1936 were taken from Kassel's review (101) or from that of Zeise (175 to 179). No attempt at a critical selection has been made, so that naturally many obsolete and incorrect results are included. The excellent critical discussion of Kassel should be consulted for the older results. Many references contain only the entropy at one or two temperatures.

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CHEMICAL EQUILIBRIA, FREE ENERGIES, AND HEAT CONTENTS FOR GASEOUS HYDROCARBONS[1]

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The statistical methods for calculating thermodynamic functions of hydrocarbons are discussed. In addition to the more common methods which are suitable for the simpler molecules, a procedure is described which is especially suited to the complex hydrocarbons and our present incomplete knowledge of their molecular constants. Agreement is obtained with all experimental data for the paraffins on the basis of reasonable rotation-restricting barriers. There appear to be inconsistencies in the data for propylene, which render somewhat uncertain the values for the higher olefins.

Tables are presented which give the heat and free-energy functions for all the paraffins through the heptanes, together with some discussion of estimates for the higher members. The simpler unsaturated hydrocarbons are also included. A few equilibrium constants and heats of reaction are calculated as examples of the use of this data.

I. INTRODUCTION

The first extensive survey of hydrocarbon thermodynamics was included in the monograph by Parks and Huffman (30), whose point of view was almost purely experimental. The point of view of statistical mechanics, which has been so useful for simple molecules, was extended to hydrocarbons by Eidinoff and Aston (9) and by Kassel (20). Their methods were based on the assumption of completely free rotation about single bonds, which led to unsatisfactory results. In 1937 the writer (32) extended their methods to allow for a sinusoidal potential barrier restricting internal rotation. It was then possible to obtain agreement with all experimental data.[2] Furthermore, the potential barriers so obtained varied in a reasonable fashion through any series of similar compounds.

Recently the writer (33) has developed somewhat different statistical

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[2] In addition to the paper already mentioned treating several hydrocarbons, the work of Smith and Vaughan (36), of Teller and Topley (39), and of Kemp and Pitzer (22) on ethane alone may be noted.

methods, which are especially suited to long-chain molecules. These have permitted extension of the work through the heptanes and some octanes. These results are included below without change, except that a wider range of temperatures is considered.

In the present paper the calculations for those saturated hydrocarbons which were included in the 1937 paper are completely revised. All of the old results agree within their assigned uncertainties with the values below; however, considerably greater accuracy can now be claimed at certain points. Although some comment will be made on the accuracy of the earlier work on the unsaturated compounds, no changes are made in the values; this arises from the lack of additional experimental evidence. An attempt has also been made to present the data in a form easily used by those not too familiar with thermodynamics.

The treatment presented below may be described essentially as follows: A picture is set up for a given molecule involving atomic masses and the geometry of the equilibrium configuration, i.e., bond angles and distances. Also needed is a knowledge of the potential energy as a function of deviations from this equilibrium position. This is assumed to be given by an expression involving bond stretching and bending force constants, and potential barriers for internal rotation. In terms of this picture it is then possible to calculate the entropy, heat capacity, and related thermodynamic functions. However, certain details of the molecular pictures are not yet known independently, and must then be obtained from experimental entropies or heat capacities with the above calculation reversed. Thus for the present at least, the final result should be regarded as based on the experimental thermodynamic data employed. However, it is possible by these calculations to give reasonably certain values of thermodynamic quantities for temperatures other than those of the measurements, and even to extend the results to other molecules. In addition, valuable information is obtained concerning the forces operating within hydrocarbon molecules.

II. MOLECULAR STRUCTURE DATA

In this section the data taken from non-thermodynamic sources will be discussed. Atomic masses are too well known to require comment. The carbon-to-carbon single-bond distance was taken as 1.54 Å. and the carbon-to-hydrogen distance as 1.09 Å. All angles were assumed to be tetrahedral. The electron diffraction results of Pauling and Brockway (31) support these values.

One of the fundamental assumptions of our treatment involves the separation of the vibration of the hydrogen atoms from the vibration of the carbon skeleton. This assumption has been made very commonly by various workers, and may be regarded for the present as necessary.

The justification is, of course, that the light hydrogen atoms move with much higher frequencies than the heavier carbon atoms, and therefore the former complete several cycles to the latter's one. Actually, certain hydrogen bending motions show about the same frequencies as carbon-to-carbon bond stretching motions. If the geometry is favorable, these motions can interact very considerably. Nevertheless, for our purpose, which is the calculation of thermodynamic functions, an error in a given frequency is not serious, provided a compensating error is made in another. Thus the neglect of interactions which raise one frequency and lower another will be satisfactory here, even though it might be fatal in spectroscopy.

For these calculations, frequencies characteristic of CH_3, CH_2, and CH groups have been selected on the basis of the spectroscopic data from simple molecules. For the methyl group the data on the methyl halides (37) and on ethane (17, 6) were considered; the stretching frequencies were taken as 3 at 3000 $cm.^{-1}$, and the bending frequencies as 3 at 1400 and 2 at 1000 $cm.^{-1}$ For the CH_2 group, the data on methylene chloride (5), formaldehyde (37), and ethylene (37) were considered; the selection was 2 at 3000, 2 at 1400, and 2 at 1000 $cm.^{-1}$ For the CH group, chloroform and bromoform (37) were considered, and the values 1 at 3000 and 2 at 1200 $cm.^{-1}$ chosen.

In the calculations on the simpler molecules the observed skeletal vibration frequencies were used (26). For the more complex hydrocarbons the force constants were employed. These were calculated from the simpler molecules, care being taken to assume consistently that the hydrogen and carbon vibrations do not interact. On this basis the value 4.1×10^5 dynes per centimeter was obtained for the carbon bond stretching constant. The bending constant was taken as 3.6×10^4 dynes per centimeter at the end of one bond length.

III. THERMODYNAMIC FUNCTIONS FOR THE SIMPLER HYDROCARBONS

By using the same methods as in the earlier papers (32), but the constants just given, thermodynamic functions were calculated for the molecules derivable from methane by substituting only methyl groups. The carbon skeleton of any of these involves no internal rotations, such rotations moving only the hydrogens of a methyl group. The formulas used for the rigid molecule are as follows:

$$(H_0^0 - F_T^0)/T = R[3/2 \ln M + 4 \ln T - \ln P + \frac{1}{2}\ln(I_1I_2I_3 \times 10^{117}) - \ln \sigma] - 10.237$$

$$(H_T^0 - H_0^0)/T = C_p = 4R = 7.948$$

$$S_T^0 = (H_0^0 - F_T^0)/T + (H_T^0 - H_0^0)/T$$

The symbols are the usual ones, I representing a moment of inertia and σ the symmetry number. The formulas and tables for internal rotation contributions were given in the 1937 paper (32). The vibrational contributions for harmonic oscillators are given in many places (27), usually under the name "Einstein functions" which are for three degrees of freedom.

The one remaining constant needed in these calculations is the height of the potential barrier (assumed to be sinusoidal in shape) restricting internal rotation. These values were selected to fit the known entropies and heat capacities of ethane (41, 24), propane (21, 23), and tetramethylmethane (2). In the latter cases the barriers for each methyl group were assumed to be equal and independent. No assumption is needed as to which is the equilibrium position. Lacking experimental data, the potential barrier must be estimated for isobutane. Since the value 3600 cal. per mole was adopted for all internal rotations in more complex molecules, it is used here even though a comparison of other molecules indicates a slightly higher value. The error from this source in the thermodynamic functions should not be greater than a few tenths of a calorie per degree. Table 1 contains the various parameters appearing in the calculations, and the entropies at 298.1°K.

TABLE 1

The various parameters appearing in the calculations, and the entropies at 298.1°K.

SUBSTANCE	CH_3CH_3	$CH_2(CH_3)_2$	$CH(CH_3)_3$	$C(CH_3)_4$
$I_1I_2I_3 \times 10^{117}$ g.^{3} cm.^{6}	18.2	336	1965	6570
$I_r \times 10^{40}$ g. cm.^{2}	2.63	4.4	5.0	5.1
V_0, in calories per mole	2800	3300	(3600)	4700
Skeletal vibration frequencies (26) in cm.$^{-1}$	993	1053	962(2)	921(3)
		867	794	732
		373	438(2)	416(3)
			370	332(2)
Symmetry number	6	2	3	12
$S^0_{298.1}$, in calories per degree mole	54.86	64.7	70.5	73.2

IV. THERMODYNAMIC FUNCTIONS FOR THE MORE COMPLEX HYDROCARBONS

When internal rotation appears in the carbon skeleton, the method of calculation commonly used ceases to be very suitable. This is because the assumption of that method, that the molecule is essentially rigid, is no longer even approximately correct. The harmonic oscillations of ordinary molecules do not change the moments of inertia much on the average, but the possible gyrations of a long-chain hydrocarbon might have considerable effect. In the 1937 paper the writer treated *n*-butane by considering the molecule in each potential minimum with respect to rotation. Such a method becomes very laborious, however, in even slightly more complex cases. A different scheme of calculation has been developed recently by the writer (33), which is more suitable for the complex hydrocarbons. The general principles of this scheme will be reviewed briefly, without pretending to repeat the derivation.

This method is based on the integral or classical form of the partition function which is approached at high temperatures (10). This equation involves only the masses of the particles and a knowledge of the potential energy as a function of their positions. It does not require knowledge of the normal coördinates of vibration and their frequencies. Actually some corrections must be made at the lower temperatures, as will be explained below. The molecules are treated first on the basis of the carbon atoms alone, assigning an effective mass. Then contributions from the hydrogen atoms of the CH_3, CH_2, and CH groups are added on.

The potential energy of the molecule is assumed to be given by an expression including the usual terms for bond stretching and bending, with the force constants given above, and a threefold sinusoidal potential barrier for each internal rotation. In addition, the potential energy of certain configurations is raised to account for steric repulsions.

With this potential energy, the expression for a thermodynamic function takes the form:

$$\begin{aligned} Th.F. = F_{0(T)} + N_1\,[\text{C—C str.}] + N_2\,[\text{C—C bend.}] + N_3\,[\text{I.Rot.}] + \\ F_{(\text{steric})} + F_{(\sigma)} + N_4\,[\text{CH}_3] + N_5\,[\text{CH}_2] + N_6\,[\text{CH}] \end{aligned}$$

where *Th.F.* represents the thermodynamic function; $F_{0(T)}$ is a function of T not depending on the molecule; [C—C str.] is a function of the C—C bond stretching constant, and N_1 is the number of such bonds in the molecule; [C—C bend.] is similarly for C—C bond bending, and N_2 is the number of such degrees of freedom; [I.Rot] is similarly for internal rotation, and N_3 the number of skeletal rotations. $F_{(\text{steric})}$ is a function of energy assigned various positions on the basis of steric repulsions, and $F_{(\sigma)}$ adjusts for the symmetry number σ in the usual manner; N_4, N_5, and N_6 are the numbers of CH_3, CH_2, and CH groups in the molecule, and [CH_3], [CH_2], and [CH] represent their contributions to the thermodynamic function in question. All terms may depend on the temperature except $F_{(\sigma)}$, and are, of course, different for the various thermodynamic functions. Values for the various terms are tabulated in the paper (33) wherein this method is developed.

In the simpler hydrocarbons the potential barriers were determined from experimental data in three cases and estimated in the fourth. The sparsity of accurate experimental data for the more complex molecules makes a different procedure desirable. Here the potential barriers and other constants will be given the same values for all molecules, and these values will be selected on the basis of the constants for the simpler molecules and the available thermodynamic data on the more complex ones. On this basis it is hoped that calculations for other molecules will have some validity.

The potential barrier expected for the rotation of a methyl group at the end of a long chain would be the same as in propane, 3300 cal. For rotations within the chain a somewhat higher value might be expected. As a simplifying compromise 3600 cal. per mole is used throughout.

For the carbon skeleton rotations it becomes necessary to decide which position is the stable one. Let us define as the *cis*-position that corresponding to a symmetry of D_{3h} in ethane. Here each hydrogen is as near as possible to one at the other end of the molecule. The *trans*-position then corresponds to an ethane symmetry D_{3d}, or a rotation of 60° from the *cis*-position. This puts a hydrogen at one end half-way between two at the other. Conn, Kistiakowsky, and Smith (4) have considered the evidence favoring either position. They consider the reasonableness of either case through a large body of thermochemical data, and conclude "unreservedly" in favor of the *trans*-position as the stable one. Somewhat different conclusions have been reached by Gorin, Walter, and Eyring (14), and for ethane alone by Karweil and Schafer (17). The range of facts considered by these authors does not compare, in the writer's opinion, with that considered by Conn, Kistiakowsky, and Smith, at least for the case of the multi-carbon systems. Consequently we shall assume the *trans*-position to be stable, yet realizing that this conclusion is not absolutely certain. The thermodynamic functions would not be greatly affected by changing this assumption.

As compared to methyl group rotations which have by symmetry a potential barrier with three equal peaks and minima, the internal rotation of a carbon skeleton is not usually symmetrical and may have peaks and minima of different heights. Thus in *n*-butane there is one planar position with the methyl groups far apart and two positions derived by 120° rotation in either direction. In these latter positions the methyl groups are a bit closer than allowed by their ordinary van der Waals or kinetic theory radii. These two positions are probably somewhat higher in energy than the planar one, because of these steric repulsions.

With the addition of more bonds the number of such positions increases rapidly. However, in the normal paraffins they can be easily classified as follows: (*1*) The planar, zigzag configuration which is presumably most stable. (*2*) Positions which involve one or more interactions of the type met in *n*-butane. They are assigned an energy *na*, where *n* is the number of interactions and *a* is the energy factor to be fixed from the available data. (*3*) Positions which involve such close approach of non-bonded atoms as to be of very high energy, and consequently excluded.

In the branched-chain compounds different situations arise. However, in order to avoid additional constants, each position was assigned an energy in terms of *a*. This somewhat arbitrary procedure was carried out with the aid of the "Fisher–Hirschfelder" models, which approximate proportional atomic sizes. Fortunately the number of different positions is less in the branched-chain isomers, because of the increased number of symmetrical methyl groups and occasional tertiary butyl groups which are likewise symmetrical. On the other hand, it was impossible to assemble a model completely in a few cases, most notably that of 2,2,4-trimethylpentane. In such cases the energy assignments are little better than a guess.

TABLE 2

Molal entropies of the normal paraffins, together with data used in their calculation
($\sigma = 2$ and $N_4 = 2$ throughout)

SUBSTANCE	N_1	N_2	N_3	N_5	NUMBER OF POSITIONS WITH ENERGY							$S^\circ_{298.1}$	
					0	a	$2a$	$3a$	$4a$	$5a$	∞	Calculated	Observed*
												cal. per degree	*cal. per degree*
Butane	3	2	1	2	1	2	0	0	0	0	0	74.17	73.7
Pentane	4	3	2	3	1	4	2	0	0	0	2	83.27	82.2[3]
Hexane	5	4	3	4	1	6	8	2	0	0	10	92.41	92.3
Heptane	6	5	4	5	1	8	18	12	2	0	40	101.54	101.3
Octane	7	6	5	6	1	10	32	38	16	2	144	110.67	110.0
Δ per CH_2	1	1	1	1	0	2						9.13	

* Experimental error about 1 calorie per degree.

Table 2 contains the assembled data for calculations for normal paraffins. The steric parameter *a* was given the value 800 cal. per mole to obtain agreement with the accurate experimental entropies of *n*-butane and *n*-heptane obtained by Aston (1) and the writer (33), respectively[3].

At their boiling points the following values were obtained: *n*-butane,—experimental, 72.0, calculated, 72.1 cal. per degree; *n*-heptane,—experimental, 111.78 ± 0.3, calculated, 111.6 cal. per degree. Since only one arbitrary constant was fixed, the agreement for both substances may be

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[3] After completion of these calculations, the writer received an unpublished value of the entropy of *n*-pentane of 83.46 ± 0.3 cal. per degree at 298.1°K., from the work of Messerly (28). The agreement with the calculated value is perfect.

said to verify the potential barrier of 3600 cal. selected above. The observed values[3] in table 2 are from Parks and coworkers (30), with vaporization data from various sources.

TABLE 3

Molal entropies of the branched-chain paraffins, together with data used in their calculation

SUBSTANCE	N_1	N_2	N_3	N_4	N_5	N_6	N_7	NUMBER OF POSITIONS WITH ENERGY						σ	$S^0_{298.1}$	
								0	a	$2a$	$3a$	$4a$	∞		Calculated (gas)	Experimental (liquid)
															cal. per degree	*cal. per degree*
2-Methylbutane	4	4	1	3	1	1	0	2	0	1	0	0	0	1	82.0	60.8
2,2-Dimethylbutane	5	6	1	4	1	0	1	1	0	0	0	0	0	1	85.7	64.4
2,3-Dimethylbutane	5	6	1	4	0	2	0	1	0	2	0	0	0	2	86.5	
2-Methylpentane	5	5	2	3	2	1	0	2	0	3	0	0	4	1	90.1	69.9
3-Methylpentane	5	5	2	3	2	1	0	2	0	2	0	2	3	1	90.0	
2,2,3-Trimethylbutane	6	8	1	5	0	1	1	1	0	0	0	0	0	1	92.3	64.8
2,2-Dimethylpentane	6	7	2	4	2	0	1	1	0	0	0	0	2	1	93.4	68.1
2,3-Dimethylpentane	6	7	2	4	1	2	0	4	0	0	0	0	5	1	98.8	72.4*
2,4-Dimethylpentane	6	7	2	4	1	2	0	2	0	0	0	2	5	2	94.7	69.7
3,3-Dimethylpentane	6	7	2	4	2	0	1	5	0	2	0	0	2	2	95.4	70.1
3-Ethylpentane	6	6	3	3	3	1	0	11	0	0	0	0	16	3	98.3	74.6
2-Methylhexane	6	6	3	3	3	1	0	2	4	3	4	0	14	1	99.5	75.3
3-Methylhexane	6	6	3	3	3	1	0	4	4	4	0	0	15	1	101.3	74.0*
2,2,3,3-Tetramethylbutane	7	10	1	6	0	0	2	1	0	0	0	0	0	6	94.1	61.4 (solid)
2,2,4-Trimethylpentane	7	9	2	5	1	1	1	2	0	0	0	0	1	1	101.4	75.2

* The experimental entropies in this table are for the liquid, except as noted. All are from the work of Parks and Huffman (30) except the data for 2,2-dimethylbutane and 2-methylpentane, which are from the work of Stull (38). Those values designated by an asterisk are especially uncertain; the others are probably self-consistent to within 1 or 2 cal. per degree and somewhat low. The substances marked by an asterisk are, interestingly, also the two cases where optical isomers occur. The calculated values include an $R \ln 2$ term to account for this fact.

When the calculations were carried out in the same fashion for the branched-chain isomers, the entropies obtained were too large. This is not surprising when one considers the high potential barriers found for tetramethylmethane, and the higher bending vibration frequencies observed in isobutane and tetramethylmethane. No account has yet been taken of these factors. Since an accurate entropy is available for only one branched-chain paraffin above neopentane, any complex way of accounting for these factors would be absurd. The following simple procedure was adopted:

Thermodynamic functions were calculated for isobutane and tetramethylmethane, using the approximate methods of this latter section, and from these were subtracted the accurate values given above. The differences obtained were then applied as a correction to the higher branched-chain isomers,—one isobutane correction being used wherever a carbon atom is bonded to three other carbon atoms, and a tetramethylmethane correction wherever a carbon atom is bonded to four others. The 2,2,4-trimethylpentane entropy now comes within 1 cal. per degree of the experimental value (33) (which has a ±0.3 cal. per degree error) and this is as high accuracy as can be expected with such compounds at this time.

Table 3 contains the assembled data for the branched-chain paraffins. The number of CH groups, N_6, is, of course, also the number of carbon atoms bonded to three other carbons; N_7 is the number of carbons bonded to four others.

The only severe test to be applied is the case of 2,2,4-trimethylpentane already mentioned. However, in the last column the available entropies of the liquids are listed. Data for conversion to the gaseous state are not available. All these entropies involve long extrapolations from 90 to 0°K., which, however, were made consistently throughout. On the other hand, the writer (33) found the 2,2,4-trimethylpentane extrapolation was 3 cal. per degree too low, while the *n*-heptane extrapolation was almost exactly right, which indicates that confidence can be placed in these values only to an accuracy of 2 or 3 cal. per degree. Actually the calculated and experimental values show remarkably similar variations, and their differences are very reasonable as entropies of vaporization.

Except for the simplest hydrocarbons (23, 24), the data on specific heats of gases are so sparse and inaccurate as to be of little value at present in checking values calculable by the methods discussed above. No serious discrepancies arise except in cases where the experimental data are very doubtful. On the other hand, no great confidence can be placed in values calculated by these methods until they have been checked experimentally. Fortunately, the likely chemical equilibrium calculations are not sensitive to the heat capacity values.

V. UNSATURATED HYDROCARBONS

Thermodynamic functions for acetylene and ethylene have been calculated by Kassel (18) and the writer (32) and are included without change.

There is some doubt as to the correct potential barrier for the methyl group rotation in propylene. On the basis of the data of Frey and Huppke (11), and of Kistiakowsky and coworkers on the hydrogenation reaction, the writer (32) obtained a result of less than 800 cal. for this quantity. Kistiakowsky, Lacher, and Ransom (23) measured the heat capacity of gaseous propylene and placed the value at about 600 to 800 cal. per mole^{-1}, in good agreement. Powell and Giauque[4] (34), taking the average as 700, obtained a third-law entropy of propylene which was 1.1 cal. per degree too low on the basis of this barrier. They attributed this discrepancy to a lack of discrimination between the CH_2 and CH_3 ends in the orientation of the molecule in the crystal. Then Crawford, Kistiakowsky, Rice, Wells, and Wilson (7) reported that the value of 700 cal. was wrong and that the correct value was about 2100 cal., a value which gives agreement with the third-law entropy. These last authors failed to discuss the results of Frey and Huppke, which can hardly agree with this last conclusion. In fact the barrier of 2100 cal. for propylene will give hydrogenation equilibrium constants differing by about a factor of 2. There seems no reason to believe Frey and Huppke's work to be in error by such a factor. On the other hand, the latest results of Kistiakowsky and his coworkers are not to be disregarded.

It is unfortunate that the third-law entropy can be said to agree with either result. In passing it might be noted that since both ends of the molecule of 2-butene are the same, there would be no uncertainty in the third-law entropy there. Either the *cis*- or the *trans*-isomer could be used to get a definite value for the potential barriers in this case.

In view of the present uncertainty there seems no justification for changing the thermodynamic functions calculated by the writer (32) in 1937 for propylene and the various butenes. On the other hand, the results must be regarded as much less certain than those for the corresponding paraffins. The errors may even exceed the 1 cal. per degree limits suggested in 1937.

Detailed calculations for the higher olefins obviously would be prema-

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[4] Professor Giauque and Dr. Powell have requested that attention be called to a numerical error in the calculation of the restricted rotation contribution to the entropy at 298.1°K. The entropy correction for hindered rotation given as -1.00 cal. deg.$^{-1}$ mole^{-1} at 298.1°K. in Table XI of their paper should have been -0.15 when a potential barrier of 700 cal. mole^{-1} is used. This leads to a value of 64.9 cal. deg.$^{-1}$ mole^{-1} for the entropy of propylene from molecular data at 298.1°K., instead of the value 64.0 which was given. However, if one agrees with Kistiakowsky that his value of 700 cal. mole^{-1} is wrong and accepts the later value of 2119 cal. mole^{-1} proposed by Kistiakowsky and coworkers, the value 64.0 cal. deg.$^{-1}$ mole^{-1} is by fortuitous circumstance about the correct answer. The value at the boiling point 225.35°K. is correct, assuming a 700 cal. mole^{-1} barrier.

ture. Estimates can be made in particular cases by considering the corresponding paraffin and the difference between the most analogous butene and butane. Also, possible differences in the heats of hydrogenation and symmetry numbers should be taken into account.

VI. TABULATION OF THERMODYNAMIC FUNCTIONS

While in many cases the thermodynamic functions calculated by the methods outlined above are not as accurate as one might desire, they are, for the most part, at least as good as the available heat of combustion data. The precision needed in the latter is, of course, much greater. All the heats of formation used in the tables to follow are from Rossini's complete review of the available data (35), except for a few branched-chain paraffins not included by Rossini. For the latter, the writer has given provisional values based on the available experimental data (30) and on empirical

TABLE 4

Thermodynamic constants for the formation of gaseous hydrocarbons at 298.1°K.

$n\text{C (graphite)} - m\text{H}_2\text{(g)} = \text{C}_n\text{H}_{2m}\text{(g)}$

SUBSTANCE	ΔS	ΔH	ΔF
	cal. per degree	*kcal.*	*kcal.*
Methane	−19.39	−17.865 ± 0.074	−12.085
Ethane	−41.61	−20.191 ± 0.108	−7.787
Propane	−64.4	−24.750 ± 0.124	−5.55
n-Butane	−87.5	−29.715 ± 0.153	−3.63
Isobutane	−91.2	−31.350 ± 0.132	−4.16
n-Pentane	−111.1	−34.739 ± 0.213	−1.62
2-Methylbutane	−112.3	−36.671 ± 0.153	−3.19
Tetramethylmethane	−121.1	−39.410 ± 0.227	−3.31
n-Hexane	−134.5	−40.01 ± 0.50	+0.08
2-Methylpentane	−136.8	−41.8 ± 0.7	−1.0
2,2-Dimethylbutane	−141.2	−44.4 ± 0.7	−2.3
n-Heptane	−158.0	−45.35 ± 0.80	+1.75
2-Methylhexane	−160.1	−47.1 ± 1.0	+0.6
2,2-Dimethylpentane	−166.2	−49.8 ± 1.0	−0.3
n-Octane	−181.5	−50.70 ± 1.0	+3.4
2,2,4-Trimethylpentane	−190.8	−56.2 ± 2.0	+0.7
n-[$\text{C}_n\text{H}_{2n+2}$] ($n > 6$)	[$-23.49n$ $+6.4$]	$-[5.35n - 7.90]$ $\pm 0.12n$	[$+1.65n$ -9.80]
Ethylene	−12.49	+12.556 ± 0.067	+16.279
Propylene	−32.8	4.956 ± 0.110	14.73
1-Butene	−55.1	0.383 ± 0.181	16.81
cis-2-Butene	−56.9	−1.388 ± 0.181	15.57
trans-2-Butene	−57.5	−2.338 ± 0.181	14.80
"Isobutene" (2-methylpropene)	−59.2	−3.205 ± 0.162	14.44
Acetylene	+14.07	+54.228 ± 0.233	50.034

TABLE

Thermodynamic functions for some gaseous paraffins

FUNCTION	T	METHANE	ETHANE	PROPANE	*n*-BUTANE	ISO-BUTANE	*n*-PENTANE	2-METHYL-BUTANE	TETRA-METHYL METHANE	*n*-HEXANE	*n*-HEPTANE	*n*-OCTANE	Δ PER CH_2
$\frac{H_0^0 - F_T^0}{T}$ in calories per degree...	298.1	36.42	45.25	52.83	58.54	56.14	64.19	64.70	56.28	69.86	75.52	81.18	5.66
	400	38.82	48.20	56.62	63.56	60.85	70.32	70.40	61.87	77.12	83.91	90.70	6.79
	500	40.72	50.72	59.98	68.02	65.13	75.80	75.64	67.13	83.63	91.46	99.29	7.83
	600	42.36	53.06	63.13	72.16	69.21	80.89	80.63	72.18	89.69	98.47	107.25	8.78
	800	45.18	57.28	69.00	79.93	76.90	90.51	90.12	81.71	101.15	111.78	122.39	10.61
	1000	47.62	61.12	74.44	87.12	83.99	99.37	98.87	90.55	111.68	123.98	136.27	12.29
	1500	52.81	69.49	86.30	102.65	99.54	118.49	118.01	109.96	134.40	150.29	166.17	15.88
$H_T^0 - H_0^0$ in kilocalories........	298.1	2.397	2.865	3.535	4.66	4.29	5.68	5.17	5.05	6.71	7.74	8.77	1.03
	400	3.31	4.27	5.59	7.43	7.08	9.12	8.63	8.56	10.83	12.54	14.24	1.71
	500	4.35	6.02	8.08	10.77	10.46	13.26	12.84	12.84	15.77	18.27	20.77	2.50
	600	5.55	8.03	11.06	14.63	14.39	18.04	17.70	17.81	21.46	24.89	28.30	3.42
	800	8.3	12.78	17.91	23.68	23.50	29.21	28.98	29.37	34.76	40.31	45.86	5.55
	1000	11.4	18.37	25.92	34.13	34.00	42.08	41.91	42.54	50.04	58.00	65.95	7.95
	1500	21.4	34.56	48.77	63.74	64.00	78.42	78.69	79.50	93.10	107.79	122.46	14.67
ΔH_0^0 of formation, in kilocalories......................		−15.96 ±0.07	−16.48 ±0.1	−19.44 ±0.15	−23.25 ±0.2	−24.52 ±0.2	−27.03 ±0.3	−28.45 ±0.3	−31.07 ±0.3	−31.05 ±0.5	−35.15 ±0.8	−39.25 ±1.0	−4.11 ±0.2

relationships found for the simpler molecules. These are assigned a 2 kcal. error in table 6.

Thermodynamic constants for the formation of the gaseous hydrocarbons from hydrogen and graphite at 298.1°K. are given in table 4. The entropies of hydrogen and graphite are taken respectively as 31.23 and 1.39 cal. per degree.

For use in calculations at arbitrary temperatures, the free-energy function $(H_0^0 - F_T^0)/T$ and the heat content function $(H_T^0 - H_0^0)$ are given for the range 298.1 to 1500°K., together with values of ΔH_0^0 of formation. These appear in tables 5, 6, and 7. Although interpolations can be made by other methods, the graphical one will probably be most satisfactory. In this regard it is suggested that the values for the higher branched-chain isomers (where values for only 298.1, 600, and 1000°K. are given) be plotted alongside those of the normal compound as an aid in drawing the curve.

Probably the most important use to be made of these results is the calculation of equilibrium constants. For the reaction:

$$a\mathrm{A} + b\mathrm{B} + \cdots = m\mathrm{M} + n\mathrm{N} + \cdots$$

the equilibrium constant

$$K = P_{\mathrm{M}}^{m} P_{\mathrm{N}}^{n} \cdots / P_{\mathrm{A}}^{a} P_{\mathrm{B}}^{b} \cdots$$

is given by the expression

$$R \ln K_T = -\Delta F/T = \sum (H_0^0 - F_T^0)/T - (1/T) \sum \Delta H_0^0 \qquad (1)$$

where the sums are over the reaction products with a plus sign and the reagents with a minus sign thus:

$$\sum (\ \ ) = m(\ \ )_{\mathrm{M}} + n(\ \ )_{\mathrm{N}} + \cdots - a(\ \ )_{\mathrm{A}} - b(\ \ )_{\mathrm{B}} - \cdots \qquad (2)$$

The values of ΔH_0^0 for elements in their standard states are zero and may be omitted, but the function $(H_0^0 - F_T^0)/T$ has a non-zero value for all substances above 0°K.

The values of the free-energy function for methane in table 5 and for acetylene in table 7 were taken from the work of Kassel (18), but have had the contributions of nuclear spin removed to correspond to the now generally accepted convention.

It is difficult to state briefly what the errors are in these functions. Errors have been assigned to the ΔH_0^0's on the basis of Rossini's work. The errors in the free-energy function may be divided roughly into two classes:—those entering at low temperatures and present at 298.1°, and those entering at higher temperatures. Where accurate experimental entropies are available, the former are largely eliminated. Thus in table 5 the error in the free-energy function is probably less than 0.1 cal. per degree in methane, and is only a few tenths in the worst cases. On the other hand, in tables 6 and 7, excepting ethylene and acetylene, the errors may exceed 1 cal. per degree. The errors entering at higher tem-

TABLE 6

Thermodynamic functions for the higher branched-chain paraffins

SUBSTANCE	$(H^0_0 - F^0_T)/T$			$(H^0_T - H^0_0)$			ΔH^0_0 OF FORMATION
	298.1	600	1000	298.1	600	1000	
	cal. per degree	*cal. per degree*	*cal. per degree*	*kcal.*	*kcal.*	*kcal.*	*kcal.*
2-Methylpentane	69.7	88.7	110.4	6.07	21.1	49.9	−32.2 ± 0.7
3-Methylpentane	69.7	88.6	110.4	6.04	21.1	50.1	−32 ± 2
2,2-Dimethylbutane	66.0	84.6	106.4	5.87	20.9	50.2	−34.6 ± 0.7
2,3-Dimethylbutane	66.3	85.4	107.3	6.02	21.3	50.3	−34 ± 2
2-Methylhexane	75.5	97.6	122.9	7.15	24.5	57.8	−36.3 ± 0.8
3-Methylhexane	77.8	99.5	124.6	6.98	24.2	57.5	−36 ± 2
3-Ethylpentane	75.7	96.8	121.5	6.74	23.8	56.9	−35 ± 2
2,2-Dimethylpentane	71.0	92.2	117.3	6.69	24.1	57.8	−38.5 ± 1.0
2,3-Dimethylpentane	76.5	97.7	122.4	6.65	23.9	57.2	−36 ± 2
2,4-Dimethylpentane	72.3	93.6	118.6	6.66	24.1	57.7	−37 ± 2
3,3-Dimethylpentane	72.8	94.3	119.4	6.73	24.2	58.0	−37 ± 2
2,2,3-Trimethylbutane	70.2	91.5	116.6	6.59	24.2	58.1	−38 ± 2
2,2,4-Trimethylpentane	76.5	100.5	128.9	7.41	27.3	65.7	−43.4 ± 2
2,2,3,3-Tetramethylbutane	69.4	93.6	122.3	7.35	27.6	66.6	−43 ± 2

TABLE 7

Thermodynamic functions for some unsaturated hydrocarbons

FUNCTION	T	ETHYLENE	PROPYLENE	1-BUTENE	*cis*-2-BUTENE	*trans*-2-BUTENE	"ISO-BUTENE"	ACETYLENE
$\frac{H^0_0 - F^0_T}{T}$ in calories per degree	298.1	44.05	54.3	62.0	60.0	59.4	57.0	40.01
	400	46.7	57.6	66.3	64.3	63.7	61.6	42.49
	500	48.8	60.6	70.2	68.2	67.6	65.6	44.56
	600	50.8	63.3	73.9	71.7	71.1	69.4	46.38
	800	54.4	68.3	80.6	78.4	77.8	76.3	49.50
	1000	57.5	72.9	86.8	84.4	83.8	82.5	52.14
	1500	64.2	82.8	100.3	97.5	96.9	95.9	57.43
$H^0_{298.1} - H^0_0$ in kilocalories		2.59	3.20	3.99	4.06	4.06	4.25	2.41
ΔH^0_0 of formation, in kilocalories		14.51 ±0.07	8.58 ±0.2	5.49 ±0.2	3.65 ±0.3	2.70 ±0.3	1.64 ±0.3	54.34 ±0.24

peratures are difficult to estimate but may amount to several per cent in either function. This percentage should be applied only to the increases over the 298.1° values. In this connection it should be noted that ΔH_0^0 is not a purely experimental quantity but is calculated using the $H_{298} - H_0$ values. Thus it is important to use ΔH_0^0's calculated with the same functions as are to be applied later.

For convenience in practical calculations the functions for graphite (3), hydrogen (12, 8), steam (13, 40), carbon monoxide (3, 15), carbon dioxide (19), and oxygen (16) have been included in table 8. All values are from the cited literature except the heat content function of graphite, which was obtained by the writer by differentiating the free-energy function.

TABLE 8

Thermodynamic functions for graphite, hydrogen, steam, carbon monoxide, and carbon dioxide

FUNCTION	T	GRAPHITE	H_2	H_2O (g)	CO	CO_2	O_2
$\frac{H_0^0 - F_T^0}{T}$ in calories per degree	298.1	0.545	24.436	37.191	40.364	43.578	42.081
	400	0.854	26.438	39.529	42.408	45.848	44.127
	500	1.180	27.965	41.316	43.963	47.681	45.691
	600	1.510	29.218	42.789	45.238	49.261	46.984
	800	2.164	31.204	45.153	47.271	51.921	49.062
	1000	2.798	32.752	47.039	48.876	54.137	50.715
	1500	4.206	35.605	50.647	51.880	58.513	53.826
$H_T^0 - H_0^0$ in kilocalories	298.1	0.251	2.023	2.365	2.073	2.240	2.069
	400	0.51	2.731	3.190	2.784	3.197	2.798
	500	0.83	3.430	4.019	3.490	4.227	3.524
	600	1.20	4.128	4.874	4.209	5.328	4.280
	800	2.07	5.537	6.669	5.701	7.697	5.855
	1000	3.07	6.966	8.583	7.258	10.233	7.499
	1500	6.0	10.696	13.89	11.363	17.02	11.77
ΔH_0^0 of formation, in kilocalories		0.00	0.00	−57.108 ±0.010	−27.18 ±0.03	−93.949 ±0.011	0.00

Equilibrium constants for a few reactions have been calculated and are given in table 9. It is beyond the scope of this paper to calculate, or to discuss the significance of the equilibria for the many reactions for which the necessary data have been given above. There are very few direct equilibrium measurements for hydrocarbon systems. The only data considered in this work so far are those on the hydrogenation of propylene and the various butenes (11). In addition, the work of Montgomery, McAteer, and Franke (29) on the butane isomerization may be mentioned. Their results indicate a constant of about 5.5 favoring isobutane, which may be compared with the value 2.5 from table 9. This difference, which corresponds to a little over 1 cal. per degree, is about the limit of error to be associated with the calculated value.

Heats of chemical reactions may be calculated in a manner analogous to that for equilibria:

$$\Delta H_T = \sum (H^0_T - H^0_0) + \sum \Delta H^0_0 \qquad (3)$$

TABLE 9

Examples of equilibrium constants calculated from the above data

REACTION	K_{298}	K_{600}	K_{1000}
n-C_4H_{10} = iso-C_4H_{10}	2.5	0.7	0.4
$C_3H_8 = C_3H_6 + H_2$	1.3×10^{-15}	1.7×10^{-4}	5
$C_3H_8 = CH_4 + C_2H_4$	7×10^{-8}	1.0	6×10^{2}
n-$C_nH_{2n+2} = C_2H_4 + n$-$C_{n-2}H_{2n-2}$ ($n > 7$)	3×10^{-10}	0.09	170
$(CH_3)_3CCH_2CH(CH_3)_2$ = iso-C_4H_{10} + iso-C_4H_8	9×10^{-8}	7	5×10^{3}
n-$C_7H_{16} = (CH_3)_2CHCH_2CH_2CH_2CH_3$	7	1.6	1.0
n-$C_7H_{16} = (CH_3)_3CCH_2CH_2CH_3$	29	0.7	0.2
n-$C_7H_{16} = (C_2H_5)_3CH$	1.1	0.4	0.3
n-$C_7H_{16} = (CH_3)_3CCH(CH_3)_2$	10	0.4	0.1

TABLE 10

Examples of heats of reaction calculated from the above data

	HEATS OF REACTION	
	ΔH_{500}	ΔH_{1000}
	kcal.	*kcal.*
$C_3H_8 = CH_4 + C_2H_4$	20.0	21.6
$C_3H_8 = C_3H_6 + H_2$	31.1	34.6
$C_7H_{16} + 11O_2 = 7CO_2 + 8H_2O$	−1074.65	−1079.56
n-$C_5H_{12} = (CH_3)_4C$	−4.46	−3.58

where the sums are as defined in equation 2. A few typical calculations are given in table 10.

The heat content function has been calculated for the unsaturated hydrocarbons only at 298.1°K. As a rough approximation the changes in heat content above this temperature may be assumed to be the same as for the corresponding paraffin. These values will be too large, particularly at the higher temperatures, but will not err grossly.

Heat content changes for a single substance are given by the function $(H^0_T - H^0_0)$, whose temperature derivative is the molal heat capacity. On the whole there is little difference between the heat capacities of isomers above room temperature.

The entropy is given by the equation:

$$S^0_T = (H^0_0 - F^0_T)/T + (H^0_T - H^0_0)/T$$

The first function is tabulated in this form; the second must be divided by the temperature and converted to small calories.

VII. COMBINED FUNCTIONS

As can be seen easily from equations 1 and 3 above, the summation of two functions in calculating an equilibrium constant or heat of reaction could be reduced to a single sum by tabulating the combined functions:

TABLE 11

Combined free-energy and heat functions

$$F^*_T/T = (H^0_0 - F^0_T)/T - \Delta H^0_0/T$$

$$H^*_T = (H^0_T - H^0_0) + \Delta H^0_0$$

FUNCTION	T	METHANE	ETHANE	PROPANE	n-BUTANE	ISOBUTANE
$\frac{F^*}{T}$	298.1	89.96	100.53	118.04	136.54	138.40
	400	78.72	89.40	105.22	121.69	122.15
	500	72.64	83.68	98.86	114.52	114.17
	600	68.97	80.53	95.54	110.92	110.09
	800	65.13	77.88	93.30	108.99	107.55
	1000	63.58	77.60	93.88	110.37	108.51
	1500	63.45	80.48	99.26	118.15	115.89
H^*	0	−15.96	−16.48	−19.44	−23.25	−24.52
	298.1	−13.56	−13.62	−15.91	−18.59	−20.23
	400	−12.65	−12.21	−13.85	−15.82	−17.44
	500	−11.61	−10.46	−11.36	−12.48	−14.06
	600	−10.41	−8.45	−8.38	−8.62	−10.13
	800	−7.66	−3.70	−1.53	+0.43	−1.02
	1000	−4.56	+1.89	+6.48	10.88	+9.48
	1500	+5.44	18.08	29.33	40.49	39.48

$$-F^*_T/T = (H^0_0 - F^0_T)/T - \Delta H^0_0/T$$

$$H^*_T = (H^0_T - H^0_0) + \Delta H^0_0$$

These can be considered to give the free energy and heat changes for the hybrid reaction:

elements (standard state, 0°K.) = compound (T°K.)

This scheme was used by Rodebush in the *International Critical Tables* and has been advocated recently by Aston (1). It has the advantage of some simplicity, although the numbers are now ordinarily larger and may change more rapidly with temperature, making interpolation and graphing more difficult. The separate functions have the important advantage of keeping errors from different sources separated. Thus when accurate heats of combustion for the higher branched-chain paraffins become available, only the ΔH_0^0 values need be changed, but this would change the whole tables of combined functions.

As an example, table 11 contains these combined functions for the paraffins through the butanes. For the elements, with ΔH_0^0 by definition zero, the separate and combined functions become identical. Anyone finding the combined functions desirable can easily construct his own table or graph in a very short time from the tables of separate functions.

VIII. CONCLUSION

In concluding, the writer wishes to recall rather carefully the purposes and point of view of this work. The principal aim was to develop a method of correlating the available thermodynamic data for hydrocarbons, which would allow interpolation and extrapolation to different temperatures, different thermodynamic functions, and different but related molecules. The accuracy of the results depends in some cases solley on the experimental thermodynamic data employed. In other cases it depends also on the accuracy of the picture drawn from molecular structure data, and on the accuracy of the statistical methods employed. In addition, by these methods certain of the missing elements in our picture of the hydrocarbon structures can be filled in.

These data should be very useful to chemists working with reactions involving these substances. The fact that hydrocarbon equilibria are so hard to measure directly makes indirect data of this type even more valuable. The information obtained with respect to internal rotation potentials, steric hindrances, etc. should be useful also in non-thermodynamic fields.

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SOME OBSERVATIONS ON THE THERMODYNAMICS OF HYDROCARBONS AND RELATED COMPOUNDS[1]

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It is shown that it is necessary to take account of potentials hindering free rotation in calculating thermodynamic functions of hydrocarbons and related compounds from the spectroscopic and molecular data. Values obtained from the third law are correct.

By using the third-law results, down to 10°K., the necessary potentials can be obtained and thermodynamic functions calculated from 300°K. to 1200°K. with the aid of the spectroscopic and molecular data. Thus $\Delta F^0/T$ values are obtained for normal butane, normal pentane, and neopentane from 300°K. to 1200°K. based on thermal data down to 10°K. obtained in this laboratory. The results on the first two make it possible to get free-energy values for the higher normal paraffins. Tables of these are given.

A discrepancy between the entropy change in the reaction $n\text{-}C_4H_{10}(g) \rightarrow \text{iso-}C_4H_{10}(g)$, as calculated from new accurate third-law data and from the measured equilibrium constants and heats of combustion, still exists.

I. GENERAL RELATIONS

A. The free energy and equilibrium constant

The best way to obtain free energies is by use of the relationships:

$$F = H - TS \tag{1}$$

$$\Delta F = \Delta H - T\Delta S \tag{2}$$

It is customary to tabulate the free energy of formation (ΔF^0) of a compound from its elements in their most common states at the temperature in question. Gases are always taken at 1 atm. in the ideal state. This quantity is related to the equilibrium constant (K) for pressures expressed in atmospheres by the equation

$$\Delta F^0 = -RT \ln K \tag{3}$$

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To calculate ΔF^0 it is necessary to know ΔH^0 and ΔS^0, the heat content and entropy of formation, respectively.

A value of ΔH^0 of formation can be obtained from accurate values of the heat of combustion of the compound and that of the elements which form it (36). Values at other temperatures can be found using the relation

$$\Delta H^0 = \Delta E_0^0 + \int_0^T \Delta C_p^0 \, dT$$

B. Entropy values from the third law

The value of ΔS^0 can be obtained by use of the third law of thermodynamics, which states that the entropy of all "perfect" crystals at the absolute zero is zero. By "perfect" is meant that they are of a regular pattern that is repeated throughout the crystal.

The thermodynamic relation for the change in entropy of a single phase with temperature is

$$S_2 - S_1 = \int_{T_1}^{T_2} C_p \, d \ln T \qquad (4)$$

where C_p is the heat capacity at constant pressure. The entropy increase accompanying a reversible change in phase is

$$\Delta S = \Delta H/T \qquad (5)$$

where ΔH is the heat absorbed in the transition.

If complete thermal data are available on the compound starting with the "perfect" crystal at about 10°K., its entropy can be calculated by the use of the relations 4 and 5. The extrapolation required in equation 4 from 0°K. to 10°K. produces a negligible error.

C. The entropy from statistical mechanics

When the energy levels for a molecule are known from its band spectrum, the entropy of the gas can be calculated (11, 7, 13, 19) by the relations

$$S_{r+v} = R \ln \sum_i p_i e^{-\epsilon_i/kT} + \frac{1}{kT} \frac{\sum_i p_i \epsilon_i e^{-\epsilon_i/kT}}{\sum_i p_i e^{-\epsilon_i/kT}} \qquad (6a)$$

$$S_t = 3/2 \, R \ln M + 5/2 \, R \ln T - R \ln P - 2.300 \qquad (6b)$$

$$S^0 = S_t + S_{r+v} \qquad (6c)$$

where ϵ_i is the energy of the i^{th} group of quantum states of the molecule and p_i is the number of states in the group. S_{r+v} is the entropy due to rotation and vibration and S_t is the translational entropy. M is the molecular weight in grams, and P the pressure in atmospheres.

It will be shown presently that, in the present state of knowledge, both thermal and molecular data are required to obtain the thermodynamic functions of hydrocarbon molecules with reasonable accuracy at high temperatures, and that neither alone is adequate.

II. THERMODYNAMIC FUNCTIONS FOR COMPLICATED POLYATOMIC MOLECULES FROM STATISTICAL MECHANICS

A. The entropy with internal rotation

Equation 6 cannot be applied to complicated polyatomic molecules, because their spectra are too complicated to allow the energies of all the states to be ascertained. Fortunately in these cases it is possible to separate the energy states of a molecule into those for rotation and those for vibration. In this case:

$$S^0 = S_r + S_v + S_t$$

The expressions for the rotational (S_r) and the vibrational entropy (S_v) are exactly like equation 6a, except that in one case only rotational states are considered and in the other only vibrational.

The vibrational contribution to the entropy is readily ascertained from tables (15) if the fundamental modes of vibration are known from the infrared and Raman spectra.

It was shown by Eidinoff and Aston (10) that there is a very simple method of obtaining the rotational entropy if the molecular dimensions are known. In complicated molecules, of which methyl alcohol is one of the simplest, there are also internal rotations. The method of Eidinoff and Aston and its extension by Kassel (19) allowed the entropy contributions due to internal as well as external rotations to be calculated simply and accurately if zero potential hindered the internal rotations.

Pitzer (30) has extended this method (in an approximate form only) to the case where potentials hinder internal rotation. Pitzer discusses his own and related methods elsewhere in this issue (32).

B. Free energy and heat content

The differences between the free energy of the gaseous compound at the temperature T and the energy at the absolute zero ($F^0 - E_0^0/T$) can be calculated from the spectroscopic and molecular data even more simply than the entropy. This quantity is given by

$$(F^0 - E_0^0)/T = -R \ln \sum_i p_i e^{-\epsilon_i/kT} + F_t^0/T \qquad (7a)$$

$$-(F_t^0/T) = 3/2\, R \ln M + 5/2\, R \ln T - R \ln P - 7.267 \qquad (7b)$$

where F_t^0 is the free energy of translation.

The corresponding difference for the heat content of the gas is given by

$$H^0 - E_0^0 = \frac{N \sum_i p_i \epsilon_i e^{-\epsilon_i/kT}}{\sum_i p_i e^{-\epsilon_i/kT}} + 5/2\,RT \qquad (8)$$

(N is Avogadro's number)

For polyatomic molecules both equations 7a and 8 can be treated in the same way as the expression for the entropy.

Equation 8 for the compound, along with values of $H^0 - E_0^0$ for the elements, can be used to get ΔE_0^0, the energy change at the absolute zero for the reaction of formation of the gaseous compound, when the heat of formation is known.

The free energy of formation is given by

$$\Delta F^0/T = \Delta E_0^0/T + \Delta(F^0 - E_0^0)/T \qquad (9)$$

The second quantity in the right-hand member of equation 9 is the difference of the quantity, defined in equations 7, between the compound and the elements which form it.

III. CHECKS ON THE VALIDITY OF THE APPROXIMATE STATISTICAL MECHANICAL METHOD

There are three ways to check the statistical method. One of these is to compare the entropy calculated according to equation 6 for the vapors of organic molecules with that obtained using the third law. A second method is to calculate ΔF^0 by the approximate statistical mechanical method (equations 7 and 9) for a gaseous reaction where the number of rotating groups changes. This value is compared with that calculated from the measured equilibrium constant by equation 3. A third method similar to the first compares calculated and measured gaseous heat capacities.

A. Comparison with third-law entropies

The application of the first method soon showed that agreement could only be obtained between the statistical mechanical method and the calorimetric method by one of two assumptions; that either the crystal was not perfect at low temperatures and the third law did not apply, or large potentials restricted internal rotation.

Table 1 lists the comparisons which have been made for reasonably complicated molecules, using thermal data down to 10°K. In column 2 of this table is listed the difference ($S_f - S_c$) between the entropy calculated on the basis of free internal rotation (S_f) and the calorimetric entropy (S_o). Column 3 lists the potential hindering each rotating group which must be assumed to obtain agreement between the statistical mechanical and calorimetric entropies. The number of such groups is given in brackets. Column 4 gives the reference to the original work.

TABLE 1

Potentials hindering internal rotation in certain compounds as ascertained from low-temperature thermal data

COMPOUND	$S_f - S_o$	POTENTIALS	REFERENCE
	calories per degree per mole	*calories*	
Methyl alcohol..........	1.75	6,400	Kassel (19)
Tetramethylmethane....	8.6	4,500(4)	Aston and Messerly (3); Pitzer (31)
Ethane.................	1.55	3,150(1)	Kemp and Pitzer (21)
Methylamine...........	1.64	3,000(1)	Aston, Siller, and Messerly (5)
Propane................	3.4	3,300(2)	Kemp and Egan (20)
Ethyl alcohol...........	3.2	3,000(1) 10,000(1)	Schumann and Aston (37)
Isopropyl alcohol.......	4.2	3,400(2) 5,000(1)	Schumann and Aston (38)
Acetone.................	0.6	1,000(2)	Schumann and Aston (38)
Dimethylamine.........	3.73	3,460(2)	Aston, Eidinoff, and Forster (1)
Dimethylacetylene......	−0.3	0	Osborne, Garner, and Yost (27)

TABLE 2

Equilibria in certain reactions which have confirmed potentials hindering internal rotation

EQUILIBRIUM	PER CENT AGREEMENT IN "K" WITH POTENTIALS IN TABLE 1	AUTHORS
$C_2H_6 = C_2H_4 + H_2$	Exact	Smith and Vaughan (39) Teller and Topley (40) Kemp and Pitzer (21) Pease and Byers (29)
$CO + 2H_2 = CH_3OH$	Exact	Kassel (18)
$C_2H_4 + H_2O = C_2H_5OH$	Exact	Schumann and Aston (37)
$(CH_3)_2CHOH = (CH_3)_2CO + H_2$	16 per cent	Schumann and Aston (38)

B. Comparison with equilibrium data

The second method has been applied to a number of gaseous reactions in which the number of rotating groups changes. In order to yield equilibrium constants in agreement with those experimentally determined, the statistical mechanical calculation had to be made on the assumption that potentials hindered the internal rotation of certain groups. The adoption of potentials of the values necessary to get agreement with the third-law entropies yielded satisfactory checks of the "statistical" with the measured equilibrium constants.

This means that the equilibrium constants calculated from equations 2 and 3, using third-law entropies, checked the experimental ones and that the third law was correctly applied to these compounds.

Table 2 lists the several equilibria which have been used for such comparisons. Without exception the third law has been substantiated, and previously estimated potentials hindering internal rotation have been confirmed. The second column of table 2 gives the average percentage difference between the observed equilibrium constants and those calculated from statistical mechanics with potentials hindering internal rotation as given in table 1 (i.e., to fit the third-law data).

TABLE 3

Potentials hindering internal rotations from gaseous heat capacities

SUBSTANCE	V	REFERENCE
	calories	
Ethane	2750	Kistiakowsky, Lacher, and Stitt (23)
Propane	3400	Kistiakowsky, Lacher, and Ransom (22)
Propylene	2120	Crawford, Kistiakowsky, Rice, Wells, and Wilson (8)
Dimethylacetylene	<500	Crawford and Rice (9)

C. Comparison with measured heat capacities

The third way to check the statistical method is to calculate the heat capacity of the gas from spectroscopic and molecular data and compare with the values found experimentally. Kistiakowsky and his collaborators have done remarkably accurate work in this field (23, 24, 8, 9). It is necessary to assume potentials hindering internal rotation, of the same magnitude as found using the third law, to obtain agreement with the experimental heat capacities. The potentials found by this method are shown in table 3.

Finally, the fine structure of perpendicular infrared absorption bands of ethane (16), methyl alcohol (6), and methylamine (42, 41) turns out to be that due to a rigid top in each case, placing the potentials hindering internal rotation greater than 2000 cal.

The accumulated evidence in favor of relatively high potentials restricting internal rotation is so great that the existence of such high potentials must be accepted as a fact. The absence of an adequate theoretical explanation (14) is a challenge, but in no way reduces the importance of the experimental evidence. One by one apparent experimental contradictions in the evidence regarding high restricting potentials have been removed. One which still remains is discussed at the end of this paper.

IV. CALCULATING THERMODYNAMIC QUANTITIES BY COÖRDINATING MOLECULAR AND THERMAL DATA

In order to calculate thermodynamic properties from the molecular data the values of these potentials must be known. At present the only way to obtain them is by comparison with the experimental thermodynamic data. This means that it is not possible to calculate thermodynamic data from the molecular and spectroscopic data alone. On the other hand, while the entropy data and heats of combustion are available to calculate free energies and equilibrium constants at room temperature for a number of simple organic compounds, including several lower hydrocarbons, the necessary heat capacity data on the gases are not available to carry out the calculation for higher temperatures. Yet it is just in the region of higher temperatures where free-energy and equilibrium data are desirable. The same may be said of heat content data. Reliable gaseous heat capacity data are not easy to obtain at high temperatures.

Yet if the third-law data are used in conjunction with the spectroscopic and molecular data, quite reliable free-energy values can be obtained for the gas over the range from 300°K. to 1500°K.

A. Evaluation of potentials empirically from third-law data

If a third-law value is available for the entropy of the gaseous compound at room temperature (or at the normal boiling point) and if the spectroscopic and molecular data are relatively complete, the potentials hindering internal rotation can be obtained so as to make the entropy calculated statistically, agree with the third-law value. These potentials are then used with the molecular and spectroscopic data to obtain the heat capacity, heat content, and free energy of the gaseous compound over the desired temperature range.

Frequently there will be more than one group whose internal rotation is hindered by potential barriers, so that only the total entropy contribution due to the groups whose rotation is hindered can be found. One therefore assumes that the potential hindering the rotation of a group depends on its environment, and assumes all the potentials but one to have values already found in other compounds. Then the remaining one can be solved for. The hindered rotation whose potential is solved for is that which has more novel features of structural environment than any of the other hindered rotations.

For example, in normal pentane there are potentials hindering the rotations of the two end methyl groups. These are taken to be equal to those in propane. Also two ethyl groups rotate about bonds joining them to the central carbon atom. The potentials hindering these rotations are solved for. It is assumed that there are three equal barriers hindering the rotation in each case. This cannot be correct, because two of the barriers are due to hydrogen and one of them is due to an ethyl group. The empirical method partly compensates for this error in subsequent calculations using the potentials and frequencies. Any error in the vibration frequencies is also partly compensated for by the empirical method.

B. Potentials from measured heat capacities

Instead of an entropy value at room temperature, measured heat capacities of the gas may be compared with those calculated from statistical mechanics and the potentials solved for.

C. Convenient thermodynamic functions for tabulation

It is the quantities $F^0 - E_0^0$ and $H^0 - E_0^0$ that are obtained from the thermodynamic and molecular data. It is convenient to regard the energy of the elements in their standard states as zero at the absolute zero, that is, for them E_0^0 is taken as zero. Then for compounds E_0^0 is equal to ΔE_0^0.

This definition makes the quantities

$$F^0 = (F^0 - E_0^0) + \Delta E_0^0 \tag{10}$$

$$H^0 = (H^0 - E_0^0) + \Delta E_0^0 \tag{11}$$

refer to the process:

elements in standard states at 0°K. = compound in standard state at T°K.

The F^0 and H^0 values for the elements at T°K. are then the $F^0 - E_0^0$ and $H^0 - E_0^0$ values, respectively.

The F^0 and H^0 values may be used exactly like ΔF^0 and ΔH^0 of formation values to compute free-energy and heat content changes in a reaction. The only difference is that in this latter system the free energy and heat content of the elements are not zero but the $F^0 - E_0^0$ and $H^0 - E_0^0$ values, respectively.

This is the system used by Rodebush in the *International Critical Tables*. It has the obvious advantage that a table of H^0 *values can be used to get sensible heats directly*. A table of heats of formation cannot be used for this purpose. "*Single thermodynamic*" functions suggests itself as a name for these quantities.

It is hoped that the practice of including these functions in tables of thermo-

dynamic quantities will become frequent. When the method outlined above is followed it is no extra labor to obtain these quantities.

V. APPLICATION OF THE METHOD TO SPECIFIC HYDROCARBONS: TETRAMETHYLMETHANE (NEOPENTANE)

Table 4 is a table of thermodynamic quantities for gaseous tetramethylmethane. As this table will not be published elsewhere it is included as an illustration of the method.

The following frequencies were chosen (3, 20, 5), the number in brackets representing the number of modes for each frequency: 335(2), 414(3), 733(1), 925(3), 3000(12), 1252(4), 1455(8), 950(8). With these frequencies the vibrational entropy of the gas was calculated at the boiling point. The entropy due to rotation of the molecule was then calculated, assuming a rigid symmetrical top with moments 186.2 × 10^{-40} g. cm.^{2} The sum of these two and that due to translation was subtracted from the measured entropy, determined in this laboratory (3), for the gas at the normal boiling point. The difference was taken as due to the four hindered rotations of the methyl groups. The reduced moments of these rotations are 5.3 × 10^{-40} g. cm.^{2} from which, using Pitzer's table (30), it was deduced that three potential minima of 5000 cal. hindered the rotation of each methyl group.

TABLE 4

Thermodynamic functions of tetramethylmethane (ideal gas at 1 atm.)*

$\Delta E_0^0 = E_0^0 = -31{,}070 \pm 330$ cal. per mole

T	$\frac{-(F^0 - E_0^0)}{T}$	$\frac{-F^0}{T}$	$\frac{+\Delta F^0}{T}$	$+H^0$
°K.	*cal. per degree per mole*	*cal. per degree per mole*	*cal. per degree per mole*	*cal. per degree per mole*
300	56.38	159.94	−10.31	−25,900
400	62.00	139.67	+23.23	−22,400
500	67.83	129.96	+43.74	−17,800
600	72.17	123.95	+58.91	−12,700
700	77.26	121.64	+69.23	−7,400
800	82.10	120.93	+77.11	−1,400
900	86.65	121.17	+83.38	+5,100
1000	90.99	122.06	+88.44	+11,900
1200	99.19	125.08	+95.87	+26,300
1500	110.49	131.20	+103.46	+48,800

* While the individual values may be in error in the first decimal place, the second decimal place is of significance if derivatives are desired.

The value of the heat of formation of the gas is found to be $\Delta H_{298.16} =$

−39,448 at 298.16°K. from the heat of combustion data of Knowlton and Rossini (24) and the newest combustion data on hydrogen (35) and graphite (35). From the spectroscopic and molecular data with the empirically determined potentials, $H^0 - E_0^0$ was calculated for tetramethylmethane at 298.16°K. and combined with the corresponding values for hydrogen and graphite. The value of ΔE_0^0 was then computed.

The spectroscopic and molecular data were then used to compute $F^0 - E_0^0/T$ and $H^0 - E_0^0$ at rounded temperatures. These combined with ΔE_0^0 gave F^0/T and H^0.

The sum of the F^0/T values for graphite (7) (five atoms) and hydrogen (six molecules) at 1 atm. (12) was subtracted from the F^0/T value in table 4 (column 3) at each temperature. This gave the $\Delta F^0/T$ values in column 4 for the reaction of formation at 1 atm. The values of $(F^0 - E_0^0)/T$ in this table are probably correct to a few tenths of a calorie per degree per mole, owing to the use of a potential hindering internal rotation chosen to fit the entropy at the normal boiling point. This can be shown to be true for any compound where the vibrational frequency assignment is even roughly correct and is one of the advantages of the method (4).

A. The free energy of the normal paraffins

For several years the efforts of this laboratory have been directed towards the evaluation of similar tables for all lower hydrocarbons. The necessary data are now available for the computation of such tables for the normal hydrocarbons. Thermal measurements down to 10°K. have recently been completed in this laboratory which yield the entropies at the normal boiling points of *n*-butane (4) and *n*-pentane (25) in the gaseous state. From these results and the data on the heats of combustion (33), tables such as table 4 have been computed.

The complete tables will be published elsewhere, but table 6 contains the values of $\Delta F^0/T$ of formation at 1 atm. over the temperature range 300°K. to 1200°K. Similar tables have already been compiled by others for methane (17), ethane (31), and propane (31). These tables were corrected to the basis of the new results for graphite (35) at each temperature. The difference

$$\Delta_n^{n+1} = \Delta F^0/T(C_{n+1}H_{2n+4}) - \Delta F^0/T(C_nH_{2n+2})$$

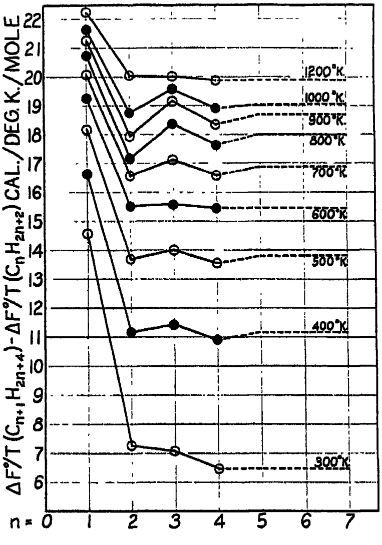
was computed between the free energies of the successive normal paraffins. Four values with $n = 1, 2, 3,$ and 4 were thus obtained from the data on the first five members at each of the temperatures. These results are tabulated in table 5 and plotted in figure 1. The alternating effect is noteworthy. The differences evidently approach constant values at about $n = 5$. The extrapolated constant difference for $n = 5$, shown in

TABLE 5

Differences in $\Delta F^0/T$ between successive members of the homologous series of normal paraffin hydrocarbons (ideal gases at 1 atm.)

$\Delta F^0/T$ for $C_{n+1}H_{2n+4}$ minus $\Delta F^0/T$ for C_nH_{2n+2}

T	$\Delta_n^{n+1} = \Delta F^0/T(C_{n+1}H_{2n+4}) - \Delta F^0/T(C_nH_{2n+2})$ IN CALORIES PER DEGREE PER MOLE				
	$n = 1$	$n = 2$	$n = 3$	$n = 4$	$n = 5$ and $n > 5$
°*K.*					
300	14.57	7.28	7.08	6.49	6.45
400	16.65	11.17	11.44	10.93	11.15
500	18.17	13.70	14.02	13.61	13.80
600	19.28	15.54	15.59	15.46	15.45
700	20.09	16.59	17.13	16.60	16.90
800	20.75	17.20	18.37	17.65	18.00
900	21.27	17.96	19.16	18.35	18.70
1000	21.66	18.76	19.58	18.92	19.05
1200	22.27	20.06	20.04	19.89	19.90



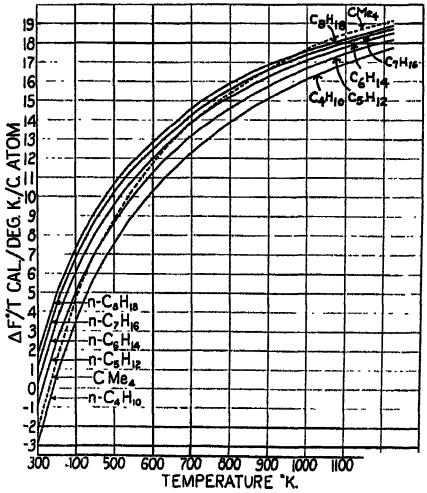


FIG. 1 FIG. 2

FIG. 1. Differences in free energy between successive paraffin hydrocarbons (ordinate) *versus* number of carbon atoms (in lower of pair). Shaded circles, odd hundreds of degrees; open circles, even hundreds of degrees.

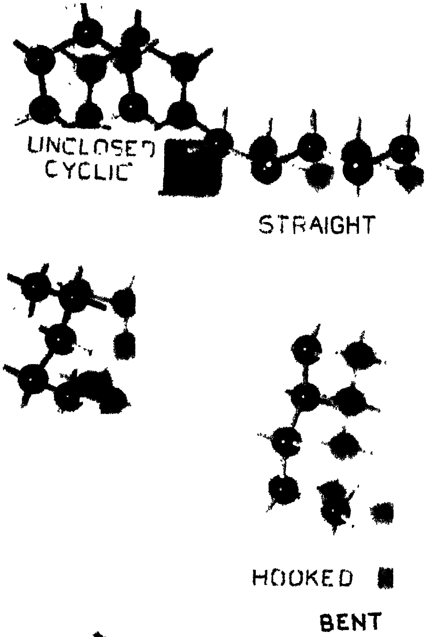
FIG. 2. Function $\Delta F^0/T$ (per carbon atom) for normal paraffins and tetramethylmethane

figure 1 and in table 5 (column 6), was used to calculate the $\Delta F^0/T$ values at each temperature for gaseous *n*-hexane, *n*-heptane, and *n*-octane from those for *n*-pentane. These values are also given in table 6.

TABLE 6

$\Delta F^0/T$ for normal paraffins (ideal gases at 1 atm.)

T	$\Delta F^0/T$ IN CALORIES PER DEGREE PER MOLE				
	C_4H_{10}	C_5H_{12}	C_6H_{14}	C_7H_{16}	C_8H_{18}
°K.					
300	−11.43	−4.94	1.51	7.96	14.41
400	+14.07	+25.00	36.15	47.30	58.45
500	+30.17	+43.78	57.58	71.38	85.18
600	+41.20	+56.66	72.11	87.56	103.01
700	+49.38	+65.98	82.88	99.78	116.68
800	+55.57	+73.22	91.22	109.22	127.22
900	+60.54	+78.89	97.59	116.29	134.99
1000	+64.51	+83.43	102.48	121.53	140.58
1200	+70.48	+90.37	110.27	130.17	150.07



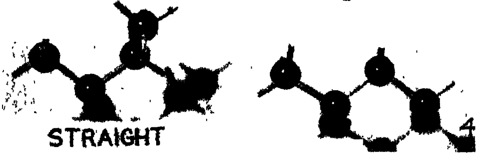


FIG. 3. The four forms of normal pentane (carbon atoms only)
FIG. 4. The two forms of normal butane (carbon atoms only)

In figure 2 the $\Delta F^0/T$ values *per carbon atom* for the gaseous normal paraffins from butane to octane are plotted against T.

It is necessary to resort to this procedure in order to obtain the $\Delta F^0/T$ values for the higher normal paraffins, not only because the vibration spectra are incomplete but because the computation becomes extremely complicated. For example, in calculating the thermodynamic functions of *n*-pentane the four forms shown in figure 3 had to be considered, whereas in the case of *n*-butane there were only the two forms shown in figure 4. The approximate ratio of each had to be computed and thermodynamic values for each had to be calculated separately. The number of such forms increases enormously as the homologous series is ascended. The $\Delta F^0/T$ values should not be in error by more than 1.5 cal. per degree per mole for octane and correspondingly less for the other hydrocarbons.

B. The effect of branching on free energy

A similar procedure to the above can be carried out for the branched-chain paraffins, when the data become available. To illustrate the effect of branching, a graph of the free energy per carbon atom for gaseous tetramethylmethane is included in figure 2. Tetramethylmethane has an increasingly higher free energy than normal pentane at higher temperatures. In other words, except below 450°K. the normal hydrocarbons are somewhat more stable than the corresponding branched-chain ones, and this extra stability increases with rise of temperature. Below 450°K. the branched-chain hydrocarbon is the more stable.

VI. THE BUTANE–ISOBUTANE EQUILIBRIUM

In this laboratory complete thermal data on *n*-butane (4) and isobutane (2) have been obtained which allow us to eliminate the extrapolation of Parks, Shomate, Kennedy, and Crawford (28). In addition, we have obtained accurate values for the heat of vaporization of both at the normal boiling point (2, 4). Thus it is possible to obtain accurate values for the entropies of the gases at 298.16°K. From these values was calculated the entropy difference

$$\Delta S = -3.66 \pm 0.2 \text{ cal. per degree per mole at } 298.16°\text{K.}$$

for the reaction

$$n\text{-}C_4H_{10} \text{ (gas)} \rightarrow i\text{-}C_4H_{10} \text{ (gas)}$$

This is to be compared with the value obtained from the equilibrium measurements of Montgomery, McAteer, and Franke (26) and the heat of isomerization found by Rossini (34). This value is −2.08 ± 0.55 cal. per degree per mole. The discrepancy of 1.58 cal. per degree per mole is outside the probable errors. It is perhaps not outside the accidental errors. If this difference were real it would necessarily indicate a failure of the third law for one or both of these compounds. Further work on the equilibrium or heat of isomerization may reduce this decrepancy, which is more than five times the maximum error in the thermal data, assuming the third law to be valid.

A similar comparison can be made for the isomeric pentanes as soon as the equilibrium data are available. Thermal data on 2-methylbutane down to 10°K. are in progress and are complete on the other two isomers (3, 25).

If the third law were not valid the method of calculating the potentials from the third-law data would fail, of course.

VII. CONCLUSION

The purpose of the foregoing review is to show that, by combining the molecular data with experimental thermal data and heats of combustion, satisfactory thermodynamic data on gaseous organic compounds may be obtained over a wide temperature range.

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SOME FREE-ENERGY DATA FOR TYPICAL HYDROCARBONS CONTAINING SIX OR MORE CARBON ATOMS[1]

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The molal free energies of formation (ΔF^0_f) at 25°C. have been calculated for about thirty typical hydrocarbons containing six or more carbon atoms in the molecule. The calculations have been made by means of the third law of thermodynamics and almost entirely with the aid of modern thermochemical data; the results, therefore, are much more accurate than similar, earlier values.

A number of correlations between molal free energy and molecular structure are deduced from the data. In the series of normal paraffins the free energies conform closely to the linear relation, $\Delta F^0_f = -8912 + 1243\ n$, where n is the number of carbon atoms in the molecule. The isoparaffins have slightly lower free-energy levels than the normal compounds. The introduction of a double bond to yield an olefin elevates the molal free energy by about 20,000 cal. The free energies of cycloparaffins come between those of the corresponding paraffins and olefins, while those of the aromatic hydrocarbons are definitely higher than the olefins. In all cyclic hydrocarbons, breaking the symmetry of the parent ring by the introduction of a paraffinic side chain first lowers the molal free energy by 1000 to 3000 cal., but subsequent increases in the length of this chain produce an increment per CH_2 group similar to that found in the normal paraffin series. The free-energy contribution of the phenyl group (C_6H_5) averages about 31,600 cal.

The third law of thermodynamics in conjunction with the fundamental equation

$$\Delta F = \Delta H - T\Delta S \tag{1}$$

has provided the only generally applicable, independent method for obtaining free-energy data for the hydrocarbons containing six or more carbon atoms. Statistical calculations of entropy and free energy have yielded extremely accurate values for many of the simpler molecules. At the present time, however, such calculations are just being developed

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for some of the more complicated molecules here involved and this development process is dependent to a high degree on accurate entropy determinations made by the third-law method (15). Moreover, equilibrium measurements, while they have yielded excellent results in a few special cases, notably in the study of the cyclohexane-methylcyclopentane isomerization by Glasebrook and Lovell (4), can constitute only an auxiliary tool in the development of a systematic set of free-energy data for the various classes of hydrocarbons.

Hence, the free energies of formation, ΔF_f^0, presented in this paper have been derived entirely through the third law. They represent the changes in the free-energy function[2] for the hypothetical process

$$\frac{m}{2}\,H_2(g) + nC\ (\text{graphite}) = C_nH_m\ (\text{l or s})^{3}$$

at 1 atm. constant pressure and 25°C. (i.e., 298.16°K.), in which the product is 1 mole of the particular hydrocarbon in the liquid or crystalline solid state, as the case may be. Most of the hydrocarbon entropies have been calculated from specific heat measurements made in the Stanford laboratory by the author and his coworkers over the temperature range from the boiling point of liquid air up to 25°C. The values for the entropies of formation, ΔS_f^0, have been derived by use of 15.615 E.U. and 1.36 E.U. for the atomic entropies of hydrogen and graphitic carbon, respectively (3, 5). The various ΔH_f^0 values have been calculated from the experimentally measured heats of combustion of the several hydrocarbons by use of 68,318 cal. (17) and 94,030 cal. (19) for the heats of combustion of hydrogen and carbon (graphite), respectively. In the past, uncertainties in the heats of combustion of organic compounds have seriously affected the accuracy of such ΔH_f^0 values, but fortunately a number of laboratories are today turning out combustion results reliable to within 0.04 per cent or better. In fact, most of the hydrocarbon combustion values utilized here are such products of this recent renaissance in thermochemistry.

The energy unit used is the *defined* conventional calorie, derived from the international joule by multiplying by the factor 1.0004/4.185. All molecular weights have been based on the 1939 table of atomic weights (1).

In connection with the tabulated free-energy data an attempt has been made to indicate roughly the reliability of the various values, at least for comparative purposes. The letter "a" after a value indicates that in the

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[2] In general, the nomenclature and symbols used in this paper are those of Lewis and Randall (10).

[3] The abbreviations used to indicate phases are as follows: g = gaseous; l = liquid; s = crystalline.

writer's judgment the maximum uncertainty is thus under 500 cal., "b" that it is under 750 cal., "c" under 1000 cal., "d" under 1500 cal., and

I. FREE-ENERGY VALUES FOR SOME PARAFFIN HYDROCARBONS

A. The normal paraffins

The normal paraffins have been studied most thoroughly and the thermodynamic functions for the members of this series are now established with reasonable accuracy up through dotriacontane ($C_{32}H_{66}$).

The molal entropies for the liquid state at 25°C. increase in linear fashion with *n*, the number of carbon atoms in the molecule. This fact

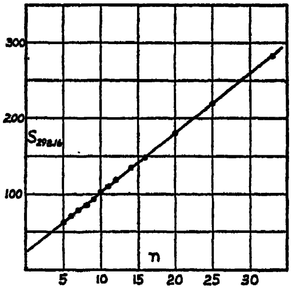

FIG. 1

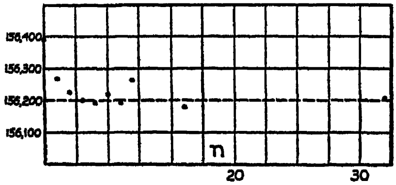

FIG. 2

FIG. 1. The molal entropies of some liquid normal paraffins plotted against *n*, the number of carbon atoms in the molecule.

FIG. 2. The combustion function $(-\Delta H_B - 57{,}250)/n$ for some liquid normal paraffins plotted against the number of carbon atoms in the molecule.

is illustrated graphically in figure 1, where the points represent experimental values and the line corresponds to the equation

$$S_{298.16} = 24.0 + 7.8n \qquad (2)$$

The heats of combustion for the liquids from *n*-hexane to *n*-dodecane, inclusive, have recently been measured with great accuracy by Jessup (6), and a comparable value for *n*-hexadecane has been reported by Richardson and Parks (16). Beckers (2) has also reported a result for crystalline dotriacontane, which should be fairly reliable. This last, subjected to our present standards for benzoic acid (7), to the Washburn (20) correction, and to conversion to combustion at 25°C., yields a value of 5,029,400 cal. for the solid state. The corresponding value in table 1 for the hypothetical liquid dotriacontane has then been derived by the addition of 26,400 cal., an estimate for the molal heat of fusion at 25°C. These molal heats of combustion for the liquid hydrocarbons containing six to thirty-two carbon atoms, inclusive, conform closely to the equation

$$-\Delta H_R = 57{,}250 + 156{,}200n \qquad (3)$$

This situation is illustrated graphically in figure 2.

In table 1 are tabulated complete thermodynamic data for nine normal paraffins. Column 2 contains the molal heats of combustion and column 3 the values for the ΔH of formation calculated therefrom. The molal entropies (S^0),—experimental values for the first eight compounds and a fairly reliable estimate in the case of dotriacontane,—and the corresponding entropies of formation appear in the succeeding two columns. Finally, the experimental values for ΔF^0_f are given in the sixth column, and corresponding values per carbon atom in the final column. These last are of especial interest in making comparisons of thermodynamic stability in a group of compounds involving different numbers of carbon atoms.

TABLE 1

Thermodynamic data for some normal paraffins at 25°C.

SUBSTANCE	HEAT OF COMBUSTION AT CONSTANT P	ΔH^0_f	S^0	ΔS^0_f	ΔF^0_f	$\Delta F^0_f/n$
	calories	*calories*	*E.U.*	*E.U.*	*calories*	*calories*
Hexane (l)	994,850	−47,560	70.9	−155.9	−1,080(a)	−180
Heptane (l)	1,150,840	−53,910	78.6	−180.8	000(a)	000
Octane (l)	1,306,850	−60,250	86.2	−205.8	+1,110(a)	+139
Nonane (l)	1,463,000	−66,450	94.0	−230.5	+2,280(b)	+253
Decane (l)	1,619,440	−72,360	102.7	−254.4	+3,490(b)	+349
Undecane (l)	1,775,360	−78,790	111.0	−278.7	+4,310(b)	+392
Dodecane (l)	1,932,380	−84,110	118.3	−304.0	+6,530(c)	+544
Hexadecane (l)	2,556,110	−109,780	148.6	−404.1	+10,710(d)	+668
Dotriacontane (l)	5,055,800	−207,650	272.7	−801.4	+31,300	+978

Since the heats of combustion and the molal entropies follow linear relations, the ΔF^0_f values calculated from these by equation 1 should follow also the linear relation

$$\Delta F^0_f = -8912 + 1243n \qquad (4)$$

This equation is represented by the line in figure 3, while the dots portray the actual experimental values.

B. *Branched-chain isomers*

The free energies of branched-chain paraffins present an interesting problem which should be investigated further. The change from the normal compound to a branched-chain isomer produces a decrease in the molal entropy; and the quantitative aspects of this effect have been worked out fairly well in a preliminary way. However, the corresponding quantitative changes in the heat of combustion with branching must now be measured very accurately in order to evaluate the effect on ΔF^0_f.

Using preliminary combustion data for the isomeric heptanes and three isomeric octanes, Parks and Huffman (13a) in 1932 were led to the conclusion that any branched-chain isomer should be on a higher free-energy level than the normal compound. However, Knowlton and Rossini's (9, 18) recent combustion values for the butane and pentane isomers have indicated that the converse is true. This situation has led to a direct study of the equilibrium in the butane isomerization by Montgomery, McAteer, and Franke (11) and to unpublished determinations of the heat of combustion and entropy of 2-methylnonane by Moore (12). All these results, presented in table 2, point to the conclusion that at room temperature the 2-methyl isoparaffin is definitely more stable (i.e., on a lower free-energy level) than the corresponding straight-chain compound.

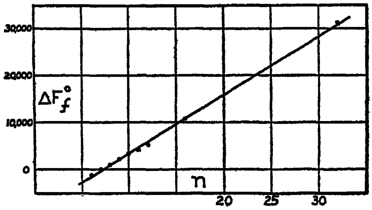

FIG. 3

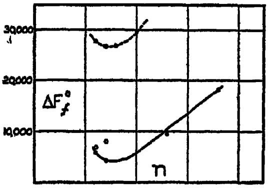

FIG. 4

FIG. 3. The molal free energies of some normal paraffins in the liquid state plotted against the number of carbon atoms in the molecule.

FIG. 4. A plot of the molal free energies of some cyclic hydrocarbons. The lower curve and dots refer to the cyclohexane series, the circles to cyclopentane derivatives, and the upper curve and dots to monophenyl benzenoid hydrocarbons.

TABLE 2

Free energy of isomerization at 25°C.

REACTION	$\Delta F^0_{298.16}$
$n\text{-}C_4H_{10}$ (l) → iso-C_4H_{10} (l)	−820 (±100)
$n\text{-}C_5H_{12}$ (l) → iso-C_5H_{12} (l)	−1020 (±400)
$n\text{-}C_{10}H_{22}$ (l) → iso-$C_{10}H_{22}$ (l)	−1490 (±670)

Similar studies, dealing with the effects of multiple branching, appear very desirable.

II. DIFFERENCES BETWEEN OLEFINS AND PARAFFINS

The withdrawal of a mole of hydrogen from a paraffin to produce an olefin hydrocarbon always raises the molal free energy considerably. In the case of the reaction

$$n\text{-heptane(l)} \rightarrow \text{1-heptene(l)} + H_2(g)$$

$\Delta F^0_{298.16}$ = 20,620 (±300) cal., according to the calorimetric studies of Kistiakowsky and coworkers (8) and the entropy measurements of Parks, Todd, and Shomate (14). Similar studies for the reaction

$$\text{tetramethylethane (l)} \rightarrow \text{tetramethylethylene (l)} + H_2(g)$$

yield $\Delta F^0_{298.16}$ = 17,100 (±700) cal. Thus with additional spatial protection to the ethylene group the olefins becomes progressively less unstable with reference to the parent paraffin hydrocarbons.

TABLE 3

Thermodynamic data for some cycloparaffins at 25°C.

SUBSTANCE	HEAT OF COMBUSTION AT CONSTANT P	ΔH^0_f	S^0	ΔS^0_f	ΔF^0_f	$\Delta F^0_f/n$
	calories	*calories*	*E.U.*	*E.U.*	*calories*	*calories*
Methylcyclopentane (l)	940,360	−33,730	59.3	−136.2	6,880 (b)	1,147
Ethylcyclopentane (l)..	1,096,440	−40,000	67.1	−161.0	8,000 (c)	1,143
Cyclohexane (l)........	936,410	−37,680	49.3	−146.2	5,910 (b)	985
Methylcyclohexane (l).	1,090,420	−46,020	59.4	−168.7	4,280 (c)	611
n-Heptylcyclohexane (l)...........	2,025,560	−84,960	106.8	−316.9	9,530 (d)	733
n-Dodecylcyclohexane (l)...........	2,809,630	−112,630	147.5	−439.1	18,290 (d)	1,016

III. FREE ENERGIES OF SOME CYCLOPARAFFINS

The saturated hydrocarbons containing five- or six-membered rings occupy free-energy levels somewhat intermediate between the corresponding aliphatic paraffins and olefins. Thus the ΔF^0_f values for methylcyclopentane and cyclohexane are 7960 cal. and 6990 cal., respectively, above that for *n*-hexane.

In table 3 appear thermodynamic data for two members of the cyclopentane series and four members of the cyclohexane series. These are based on accurate combustion and entropy determinations recently made in the Stanford laboratory by Moore and Renquist (12). The ΔF^0_f results are also plotted in figure 4.

While it is evident that more members of these two series should be studied, two facts stand out in a consideration of the data for the cyclohexane family: (*a*) Breaking the symmetry of the ring in cyclohexane to produce the methyl derivative produces a marked drop in ΔF_f^0. (*b*) Progressive increases in the aliphatic side chain on the ring cause an increase in ΔF_f^0 similar to that found with the normal paraffins. Thus the average increment in free energy per CH_2 group between methylcyclohexane and dodecylcyclohexane is 1270 cal., as against about 1240 cal. in the normal paraffin series.

In passing, it is worth noting that these third-law values yield $\Delta F_{298.16}^0 = 970$ cal. for the isomerization reaction

$$\text{cyclohexane (l)} \rightarrow \text{methylcyclopentane (l)}$$

in excellent agreement with the result, 1150 cal., obtained by Glasebrook and Lovell (4) from their direct equilibrium measurements.

TABLE 4

Thermodynamic data for some aromatic hydrocarbons at 25°C.

SUBSTANCE	ΔH_f^0	S^0	ΔS_f^0	ΔF_f^0	$\Delta F_f^0/n$
	calories	*E.U.*	*E.U.*	*calories*	*calories*
Benzene (l)	11,200	41.9	−59.9	29,060 (c)	4,843
Toluene (l)	3,520	52.4	−82.0	27,970 (c)	3,996
Ethylbenzene (l)	−3,430	61.3	−105.7	28,090 (c)	3,511
n-Butylbenzene (l)	−16,630	76.9	−155.3	29,670 (d)	2,967
Diphenyl (s)	23,250	49.2	−123.3	60,010 (d)	5,001
1,3,5-Triphenylbenzene (s)	52,920	87.9	−225.8	120,240 (e)	5,010
Naphthalene (s)	18,030	39.9	−98.6	47,430 (b)	4,743
β-Methylnaphthalene (s)	7,990	48.8	−122.3	44,450 (b)	4,041
Anthracene (s)	26,740	49.6	−125.6	64,190 (c)	4,584
Phenanthrene (s)	16,940	50.6	−124.6	54,090	3,864
Pyrene (s)	26,900	51.4	−126.5	64,620 (c)	4,039

IV. FREE ENERGIES OF SOME AROMATIC HYDROCARBONS

While entropy determinations have been made for about thirty aromatic hydrocarbons, the corresponding combustion data are in many cases inadequate for an accurate evaluation of ΔF_f^0 by equation 1. In table 4, however, appear thermodynamic (13b, 16) data for eleven compounds, which at least serve to indicate the general trends among the monophenyl and polyphenyl aromatics.

The four ΔF_f^0 values for benzene and its monophenyl derivatives are a revision of the earlier calculations of Parks and Huffman. They indicate that the general free-energy level for this series is about 23,000 cal. above the corresponding cyclohexane compounds. Here, as also in the cases of cyclohexane and naphthalene, a break in the symmetry of the parent molecule to introduce side chains on the ring causes an appreciable initial drop in the molal free energy.

With 27,000 cal. as the approximate *basic* free energy of the benzene molecule in forming derivatives, the free-energy values for diphenyl and triphenylbenzene here yield 33,000 cal. and 3 × 31,100 cal., respectively, for the introduction of additional phenyl groups.

In the case of the cyclic series benzene–naphthalene–anthracene the data show increases in ΔF_f^0 of 18,370 cal. and 16,760 cal., respectively, for each C_4H_2 increment involving the successive production of an additional ring within the molecule.

V. CONCLUSION

It is hoped that this brief review of the free energies of formation of some hydrocarbons containing six or more carbon atoms within the molecule has served to indicate the relative free-energy levels at room temperature for the various types and the general trend of the ΔF_f^0 values with structural changes. However, these problems evidently merit much additional study, as do also the problems connected with the application of such free-energy data to reactions at more elevated temperatures.

TABLE 5

Free-energy values for typical hydrocarbons at 25°C.

SUBSTANCE	FORMULA	ΔF_f^0
n-Decane (l)	$C_{10}H_{22}$	+3,490 (b)
2-Methylnonane (l)	$C_{10}H_{22}$	+2,000 (b)
1-Decene (l)	$C_{10}H_{20}$	+24,100 (*estimated*)
n-Butylcyclohexane (l)	$C_{10}H_{20}$	+7,000 (*estimated*)
n-Butylbenzene (l)	$C_{10}H_{14}$	+29,670 (d)
Naphthalene (s)	$C_{10}H_8$	+47,430 (b)

To summarize the present findings on a comparative basis, table 5 has been prepared, partly from actual experimental values and partly from estimates made with the aid of the observed regularities, for typical compounds containing ten carbon atoms in the molecule.

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STRUCTURE AND CHEMOTHERAPEUTIC ACTIVITIES OF SULFANILAMIDE DERIVATIVES[1]

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CONTENTS

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[1] This paper was presented in part before Section C of the American Association for the Advancement of Science at the Research Conference in Chemistry which was held at Gibson Island, Maryland, July, 1939. It has been revised and enlarged under the sponsorship of the Division of Medicinal Chemistry of the American Chemical Society. The author wishes to express his appreciation of the fine spirit of coöperation shown by members of the Division and others in supplying much hitherto unpublished data. He also wishes to thank M. E. Darken for aid in compiling data.

A. Introduction

The discovery of the antistreptococcic activity of azo dyes derived from sulfanilamide in the laboratories of the I. G. by Mietzsch, Klarer, and Domagk, coupled with the later work at the Pasteur Institute by the Tréfouëls, Nitti, and Bovet, which showed that the activity resided in the sulfanilamide part of the molecule, is beyond doubt the greatest contribution to chemotherapy yet made. It surpasses Ehrlich's discoveries, which were limited to the field of trypanosome diseases, since it has already led to cures of most of the common infectious diseases of bacterial origin. The discovery stimulated intensive work on sulfanilamide derivatives and allied compounds by almost every large pharmaceutical concern and medical institution in the world.

The frenzied research of the past five years has resulted in the synthesis and disclosure of about thirteen hundred new compounds derived from the parent sulfanilamide. When allied compounds and undisclosed sulfanilamide derivatives are added to these, it is probable that more than three thousand new compounds are available for chemotherapeutic study. Almost every class of sulfanilamide derivative has now been explored. Inevitably, there has been an enormous duplication in synthesis, so that often four or more groups have synthesized the same compound, independently, and within a few days or weeks of each other.

While sulfanilamide derivatives have been well explored from the chemical side, the bacteriological and pharmacological studies have been superficial and wholly inadequate. Obvious reasons for this are that pharmacologists have had a great amount of work in widening the field of usefulness of sulfanilamide and its commercial derivatives, in investigating the numerous toxic reactions, and in laying a foundation of test methods. Each new derivative calls for several weeks' work at a cost of many experimental animals before even a preliminary estimation of its therapeutic value against a single disease can be given. When this is multiplied by the number of diseases now known to be susceptible to treatment by this group of drugs, it will be appreciated that each pharmaceutical chemist should be backed by a staff of at least ten bacteriologists and pharmacologists if they are to keep pace with synthesis in this field. Unhappily the ratio is apt to be the reverse!

Marshall (128) has recently summarized experimental infections treated by the new chemotherapy as follows: "The therapeutic effect of sulfanilamide (or allied compounds) is excellent in experimental mouse infections due to the β-hemolytic streptococcus, meningococcus, and pneumococcus. It is still good, but less satisfactory in mouse infections produced by strains of gonococcus and staphylococcus; Proteus, colon, typhoid, and paratyphoid organisms; the Sonne strain of the dysentery bacillus; a strain of Listerella; Hemophilus influenzae, the Welch bacillus, and certain members of the Pasteurella group, including the plague bacillus. Prolongation of life, with few or no survivals, is reported for infections produced by strains of Salmonella typhimurium, Friedländer's bacillus; Pasteurella pseudotuberculosis and the anthrax bacillus. A definite inhibitory effect on the development of experimental tuberculosis in the guinea pig and rabbit, an alteration of the natural course of experimental Brucella infections in guinea pigs and Bacterium necrophorum infection in rabbits, and the remarkable curative effect in certain human urinary tract infections also attest to the widespread antibacterial powers of the sulfonamide group of drugs. In protozoan infections, the only conclusive evidence of effectiveness is that reported for malarial infection of monkeys. In virus infections, the results so far obtained are negative or inconclusive, with the exception of lymphogranuloma venereum and trachoma. In both of these cases, there is some doubt if the infecting agent can be classed as a true virus."

B. Measurement of Chemotherapeutic Activity

For obtaining preliminary data on the activity of a new sulfanilamide derivative, the mouse is used as a test animal almost exclusively. This is because of the ease with which mice can be handled, their low cost, and their susceptibility to infection with many of the bacteria causing human diseases. As yet, there has been no well-standardized technique which has been universally used. As a consequence, the published results of different laboratories testing the same drug have differed widely in their estimations of therapeutic value. Variations in the strain, virulence, or number of infecting organisms, in the size and frequency of dosage, and in the method of administering the drug greatly influence the survival of the mice. There has been great variation also in the length of time allowed before reading survivals and in the manner of expressing results.

Marshall's laboratory (120) has recently established a more nearly quantitative method of evaluation, based on the drug-diet method of dosage worked out by Bieter, Larson, Levine, and Cranston (13).

This method has been summarized by Marshall (128) as follows: "A more or less constant blood concentration of drug during the period of therapy is maintained by using food in which the drug has been incorporated. By treating mice in individual cages, the daily drug intake of each mouse can be determined. Drug diets are so selected that one may expect to obtain with different drug intakes survival percentages greater and less than fifty. The diets are fed for one or more days prior to and for the desired period after infection. Irrespective of the percentage drug in any diet, the average daily drug intakes (per mouse) can be arranged in groups and correlated with percentage survivals. The dosage-survival curve is now computed and the *Median Survival Dose* ($S.D._{50}$) with its standard error obtained. This can be converted into the Median Survival Blood Concentration ($S.B.C._{50}$) by a factor which relates blood concentration to daily drug intake of the drug being tested. By using a standard, one obtains a comparative value for the $S.B.C._{50}$'s which may be nearly absolute, even though the $S.B.C._{50}$'s themselves are variable."

The disadvantages of this method are the large number of individual mouse cages required for any extensive program of testing, and the tedious weighings and calculations involved. However, the advantages of obtaining reliable results instead of a mass of conflicting and uninterpretable data should far outweigh the extra space and labor required. It is to be hoped that this or a similar method may be universally adopted, so that future publications on chemotherapeutic activities may be of more value than the morass of misinformation now available.

For purposes of correlating chemical constitution with chemotherapeutic effect, much more information is desirable than has been obtained heretofore from ordinary tests in mice. It is highly useful to the chemist in projecting new syntheses to know whether a compound which has failed to protect mice against the infection is inherently inactive, or whether the lack of protection is caused by one or more of the following factors:

(*1*) The drug is rapidly absorbed and eliminated, so that effective blood concentrations are not maintained. This is undoubtedly an important factor with many highly soluble sulfanilamide derivatives; however, it does *not* follow that high water-solubility means that the compound *will* be absorbed and eliminated rapidly.

(*2*) The drug is not absorbed rapidly enough to reach effective blood concentrations. This may be caused by lack of solubility in both water and lipoids, or by other mechanisms.

(*3*) The drug is rapidly conjugated by the animal, and hence does not exist in an active form long enough to exert its chemotherapeutic effect. This is probably a minor factor, although important differences in rate of conjugation have been noted.

(*4*) The drug is toxic to the host.

The chief advantages of expressing results in terms of S.B.C.$_{50}$'s from the chemist's point of view is that, by so doing, factors 1 and 2 are eliminated and he is given a basis for comparison of inherent activities against structural characteristics or other properties of the compounds. Effects of factors 3 and 4 become apparent, also, since blood level studies in control animals will automatically demonstrate conjugation and toxicity. Fortunately, in all cases where the sulfanilamide derivative has a free amino group, or can be converted by reduction or hydrolysis to give a free amino group, blood levels of the drug can readily be determined by the method of Marshall and Cutting (130) or that of Bratton and Marshall (15).

Some further light on whether the compound is inherently active or inactive is obtained by *in vitro* bacteriostatic tests, but too much reliance cannot be placed in the results, since a multitude of factors may affect the results and not all of these are known. Also, the animal body is capable of transforming many compounds which are inactive *in vitro* to active compounds *in vivo*, as witness the original Prontosil.

The preliminary studies in mice tell almost nothing about the complications which may be encountered in human therapy with the compound, so that, after favorable results have been obtained in mice, it is necessary to conduct very extensive pharmacological and toxicological studies using larger test animals before proceeding to clinical studies. The possible dangers and the means of testing against them have been adequately covered elsewhere (122, 139, 158, 17, 128) and do not concern us here.

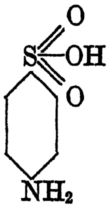
It has been the practice to compare the chemotherapeutic activities of new derivatives with the parent sulfanilamide against β-hemolytic streptococci. Lately, this has been broadened to include a comparison with sulfapyridine against pneumococci. However, if the compound is inactive by these tests, its future is apt to be a small niche in Beilstein. This is probably not a just fate, since it is by no means certain that a compound which is inactive against one or two test organisms will be inactive against all other bacteria, or even different strains of the same organism. From the commercial point of view, this is likewise a questionable procedure, since new derivatives to compete successfully with sulfanilamide must offer important advantages. That a derivative will be found which offers such advantages for the treatment of β-hemolytic streptococcic infections appears increasingly unlikely. On the other hand, new derivatives are assured of immediate commercial success if they cure diseases against which sulfanilamide is not particularly effective. The case of sulfapyridine is a pertinent example of this, since it offers little advantage over sulfanilamide against streptococci and is fundamentally a much more expensive compound to produce. It therefore would have had little chance of finding a market, were it not specific for pneumonia.

In spite of these objections, the preliminary evaluation of new compounds will continue much as at present, since any other course would soon get out of hand. It is to be hoped, however, that when chemical activity decreases, pharmacologists may make the effort to reëxamine many of the compounds passed over in the first hurried survey. It should be remembered that sulfanilamide was interred in Beilstein over thirty years ago. How many other compounds are awaiting resurrection?

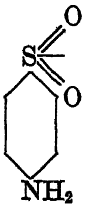
From the foregoing, it will be appreciated that there is comparatively little pharmacological data with which one can correlate the structures of sulfanilamide derivatives. This review has as its main function, therefore, the classification of the known sulfanilamide derivatives according to their chemical structures. Where available, the activity of the derivatives, as compared with sulfanilamide, against β-hemolytic streptococci has been indicated. These results are usually based on preliminary tests in mice and are not particularly trustworthy, as may be gathered from the comments above. As used herein, the signs have the following meaning: +++, slightly superior to sulfanilamide; ++, about equal to sulfanilamide; +, moderate activity; ±, very slight or uncertain activity; 0, no activity; −, toxicity (treated animals dead before the controls).

C. CHEMICAL CLASSIFICATION AND NOMENCLATURE

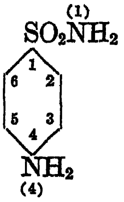
The present paper is strictly limited to derivatives of sulfanilamide. It therefore excludes the therapeutically active diaminodiphenylsulfones and other closely related compounds. The system of listing is based on the nomenclature proposed by the author and coworkers (35), which has been generally accepted in this country. The parent compound is sulfanilic acid (I),



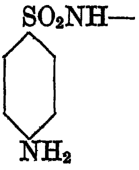
I



II

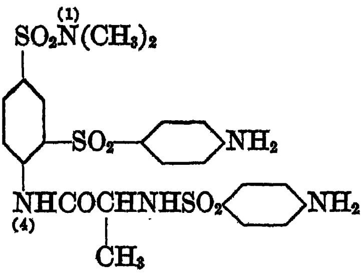


III



IV

which gives rise to the acid radical "sulfanilyl" (II) and to "sulfanilamide" (III), which in turn gives rise to the radical "sulfanilamido" (IV). Simple derivatives are best named as derivatives of sulfanilamide, and to distinguish between the nitrogens, substituents of the amido group are called N^1-substituents, while those of the amino group are N^4-substituents. As an example illustrating the usefulness of the radicals, the compound V may be named N^1,N^1-dimethyl-N^4-(2-sulfanilamidopropionyl)-3-sulfanilylsulfanilamide.



For the purposes of this paper, sulfanilamide derivatives are classified as follows:

I. Nuclear-substituted sulfanilamides.
II. N^1-Substituted sulfanilamides.

III. N^4-Substituted sulfanilamides.
IV. Nuclear,N^1-substituted sulfanilamides.
V. Nuclear,N^4-substituted sulfanilamides.
VI. N^1,N^4-Substituted sulfanilamides.
VII. Nuclear,N^1,N^4-substituted sulfanilamides.
VIII. Salts of sulfanilamide.
IX. Unclassified sulfanilamide derivatives.

Each of the above main divisions is further subdivided into the following:

(A) Inorganic substituents.
(B) Acyclic substituents.
(C) Isocyclic substituents.
(D) Heterocyclic substituents.
(E) Acyl substituents.
(F) Sulfonyl substituents.
(G) Anils (Schiff bases).
(H) Azo derivatives.

Further subdivisions follow the system in Beilstein as closely as practicable.

In the case of multiple substituents, the compound is listed under the substituent having the highest numerical and alphabetical placement above. For example, compound V (above) belongs to division VII (nuclear,N^1,N^4-substituted sulfanilamides). It would be listed under subdivision E (N^4-acyl substituents) and then under N^4-amino-acyclic-acyl substituents, according to carbon content. In a series involving the same N^4-group, it would next be classified according to the N^1-substituents, and finally according to the nuclear substituents.

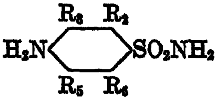
D. Sulfanilamide Derivatives

I. NUCLEAR-SUBSTITUTED SULFANILAMIDES

Nuclear-substituted sulfanilamides (see table 1) have not been investigated particularly well from either the chemical or the pharmacological side. Two reasons for this are: first, that nuclear substituents are somewhat more difficult to synthesize than are the nitrogen-substituted derivatives, and second, that the simple derivatives so far made have practically no activity. Thus, introduction of a halogen, amino, sulfonamido, methyl, or carboxyl group into the sulfanilamide ring completely destroys the activity. However, the conclusion should not be drawn that *any* substitution of the ring will destroy activity, since 3,5-dimethylsulfanilamide (155) is said to have some activity, as also aniline-3,5-disulfonamide (which, however, is not a sulfanilamide derivative).

TABLE 1

Nuclear-substituted sulfanilamides



R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
A. Inorganic substituents					
Cl—	H	H	H		(80)
H	Cl—	H	H		(173)
H	Br—	Br—	H	0	(20, 64)
H	I—	H	H		(167)
H	I—	I—	H		(167)
H	NO_2—	H	H		(55, 97, 181)
H	NO_2—	NO_2—	H	0	(161)
HO—	H	H	H	0	(181)
H	NH_2SO_2—	H	H	0	(55, 86)
H	NH_2SO_2—	NH_2SO_2—	H	0	(20, 125)
H	NH_2—	H	H	0	(61, 86, 181)
NH_2—	H	NH_2SO_2—	H		(125)
B. Acyclic substituents					
CH_3—	H	H	H	0	(86, 181)
H	CH_3—	H	H	0	(61, 155, 181)
CH_3—	H	CH_3—	H		(80, 84)
CH_3—	H	Cl—	H		(84)
H	CH_3—	CH_3—	H	+	(155)
CH_3—	H	CH_3O—	H		(81, 84)
CH_3—	H	C_2H_5O—	H		(81)
H	CH_3O—	H	H		(173)
CH_3O—	H	H	H		(80)
CH_3O—	H	CH_3O—	H		(84)
H	HOOC—	H	H	0	(57, 95)
HOOC—	H	H	H	0	(95)
C. Isocyclic substituents					
None					
D. Heterocyclic substituents					
None					

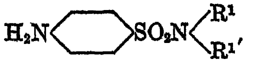
Mention has been made of the anthelmintic activity of 2-methyl-5-methoxysulfanilamide against ascarides (81).

II. N^1-SUBSTITUTED SULFANILAMIDES

This class of sulfanilamide derivatives contains practically all of the therapeutically important new derivatives and has therefore been extensively studied. Because of the number of compounds, the discussion will parallel the chemical subdivisions.

(*A*) *Inorganic substituents*

The derivative of hydroxylamine is claimed to be active, while the derivative of sulfamic acid is inactive. Scarcity of inorganic amino intermediates accounts for the few compounds in this class.



R¹	R¹′	ACTIVITY	REFERENCES
HO—	H	++	(113)
NaO_3S—	H	0	(121)

(*B*) *Acyclic substituents*

The ready availability of the aliphatic amines, hydroxyamines, and amino acids accounts for the many derivatives in this class (see table 2). In general, the compounds are of low activity. The series of N^1-alkyl- and N^1,N^1-dialkyl-sulfanilamides shows activity almost equal to sulfanilamide for the first two members, but a drop to negligible activity for carbon chains longer than three.

N^1-Hydroxyalkyl- and N^1-carboxyalkyl-sulfanilamides have given variable results in the hands of different investigators. This is probably because of rapid absorption and elimination, so that when compared with sulfanilamide the results are poor if given at the same dosage, and reasonably good if given frequently enough. In spite of the low activities reported in this country for *N*-sulfanilylglycine, it is interesting to note that it has found sale in Sweden under the name Streptasol (5, 51).

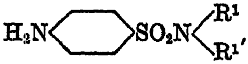
Esterification of N^1-hydroxy- or N^1-carboxy-alkylsulfanilamides destroyed their activity (42).

(*C*) *Isocyclic substituents*

These have been synthesized in great variety, since the intermediates are commercially available from the dye industry, or can readily be made from commercial intermediates. For convenience, this class is further subdivided as follows: (*1*) $R = C_nH_{2n-1}$ to C_nH_{2n-13}; (*2*) oxy and oxo derivatives; (*3*) carboxy derivatives; (*4*) sulfo derivatives; (*5*) amino derivatives; and (*6*) miscellaneous derivatives.

TABLE 2

N^1-Acyclicsulfanilamides



R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
CH_3—	H	++	(61, 86, 121, 181)
CH_3—	CH_3—	++	(26, 61, 80, 86, 164, 181)
CH_3CH_2—	H	++	(61, 86, 181)
CH_3CH_2—	CH_3CH_2—	++	(61, 70, 86, 181)
$CH_3(CH_2)_2$—	$CH_3(CH_2)_2$—	±	(61, 181)
$(CH_3)_2CH$—	H	±	(61, 181)
$CH_3(CH_2)_3$—	H	±	(61)
$CH_3(CH_2)_3$—	$CH_3(CH_2)_3$—	±	(61)
$CH_2{=}CHCH_2$—	H	+	(61, 181)
$CH_3(CH_2)_7$—	H	0	(40, 54)
$CH_3(CH_2)_{11}$—	H	0	(40, 54)
$CH_3(CH_2)_{17}$—	H	0	(40, 54)
$CH_3(CH_2)_7CH{=}CH(CH_2)_8$—	H	0	(40, 54)
$HOCH_2$—	H		(193)
$HOCH_2CH_2$—	H	+	(2, 9, 11, 42, 86, 114)
$HOCH_2CH_2$—	CH_3—	0	(40, 121)
$HOCH_2CH_2$—	$HOCH_2CH_2$—	++, +	(2, 42, 87, 121, 100)
$CH_3(CH_2)_{10}COOCH_2CH_2$—	H	0	(40)
$HOCH_2CH_2CH_2$—	H	±	(2, 114)
$CH_3CHOHCH_2$—	H	0, ±	(2, 42, 114)
$(CH_3)_2COHCH_2$—	H	0, ±	(42, 121)
$HOCH_2CH(OH)CH_2$—	H	0	(2, 114)
$CH_3CH(OH)CH_2$—	$CH_3CHOHCH_2$—	±	(42)
$C_2H_5CHOHCH_2$—	H		(114)
$(HOCH_2)(CH_3)_2C$—	H		(40)
$(HOCH_2)_2CH$—	H		(114)
$(HOCH_2)_2(CH_3)C$—	H		(40)
$HOOCCH_2$—	H (Streptasol)	±	(9, 11, 21, 32, 80, 96, 100, 102, 136)
$NaOOCCH_2$—	H	±	(21, 95, 121)
$C_2H_5OOCCH_2$—	H	±	(40)
$HOOC(CH_3)CH$—	H		(136)
$NaOOCCH_2CH_2(HOOC)CH$—	H	±	(21)
$C_4H_9OOCCH_2CH_2\underset{\vert}{C}HCOOC_4H_9$	H	0	(40)
$HO_3SCH_2CH_2$—	H		(82)
$H_2O \cdot NaO_3SCH_2CH_2$—	H	0	(121)
$(C_2H_5)_2N(CH_2)_4$—	H		(28, 29, 45)
$CH_3[(C_2H_5)_2N]CHCH_2CH_2$—	H		(28)

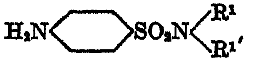
(1) N^1-Isocyclicsulfanilamides: R = C_nH_{2n-1} to C_nH_{2n-13}

These compounds are summarized in table 3, together with some of their halogen and nitro derivatives.

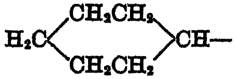
N^1-Cyclohexylsulfanilamide was found to be inactive, while N^1-phenylsulfanilamide was claimed by Buttle (20) to be as active as sulfanilamide. This claim has been disputed by others, but is historically important in that it may have given impetus to the synthesis of isosteric derivatives in the heterocyclic series leading to the very active derivatives sulfapyridine, sulfathiazole, and sulfadiazine. It is interesting to observe that Gelmo (66), who first synthesized sulfanilamide, also synthesized N^1-phenylsulfanilamide and its homologs.

TABLE 3

N^1-Isocyclicsulfanilamides: R = C_nH_{2n-1} *to* C_nH_{2n-13}



$H_2NC_6H_4SO_2N(R^1)(R^{1\prime})$

R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
 $H_2C(CH_2CH_2)_2CH—$	H	0	(70, 86)
$C_6H_5—$	H	+, ++	(20, 66, 102, 163, 181)
$C_6H_5—$	$HOCH_2CH_2—$	++	(42)
$2\text{-}ClC_6H_4—$	H	0	(42)
$4\text{-}ClC_6H_4—$	H	0	(42)
$2\text{-}(NO_2)C_6H_4—$	H		(76)
$3\text{-}(NO_2)C_6H_4—$	H		(76, 187)
$4\text{-}(NO_2)C_6H_4—$	H	+++, ±	(9, 11, 76, 102, 187)
$2,4\text{-}(NO_2)_2C_6H_3—$	H		(48)
$2\text{-}(CH_3)C_6H_4—$	H		(66, 91)
$3\text{-}(CH_3)C_6H_4—$	H		(66)
$4\text{-}(CH_3)C_6H_4—$	H		(66)
$C_6H_5CH_2—$	H	±	(68, 86, 181)
$1\text{-}C_{10}H_7—$	H		(66)
$2\text{-}C_{10}H_7—$	H		(66)

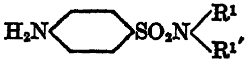
Substitution of chlorine in the phenyl ring destroys activity. N^1-(4-Nitrophenyl)sulfanilamide has been claimed to be more active than sulfanilamide, but also much more toxic. This is contradicted by Kolloff (102), who reports little or no activity for this compound in both streptococcic and pneumococcic infections.

(2) N^1-Isocyclicsulfanilamides: oxy and oxo derivatives (see table 4)

The sulfanilamidophenols as a class have little if any activity against streptococci. Sulfanilamidoguaiacol is also inactive against pneumococci (54).

TABLE 4

N^1-Isocyclicsulfanilamides: oxy and oxo derivatives



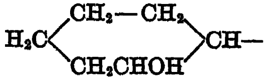
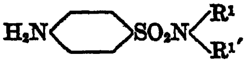
R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	0	(2)
2-$(HO)C_6H_4$—	H	—, 0	(42, 121, 187)
3-$(HO)C_6H_4$—	H	±	(121, 187)
4-$(HO)C_6H_4$—	H	++, ±	(42, 121, 127, 187)
4-HO-3-$(NO_2)C_6H_3$—	H	0	(121)
2-$(CH_3O)C_6H_4$—	H	0	(42, 54)
4-$(CH_3O)C_6H_4$—	H		(28, 29)
4-$(C_2H_5O)C_6H_4$—	H	±	(181)
3-CH_3O-4-$(HO)C_6H_3$—	H	0	(42, 54)
2-CH_3-4-HO-5-$[(CH_3)_2CH]C_6H_2$—	H	0	(42, 54)
4-$(CH_3CO)C_6H_4$—	H		(197, 145, 158)
4-$(CH_3CH_2CO)C_6H_4$—	H		(197)
4-$(C_6H_5CO)C_6H_4$—	H		(197)

TABLE 5

N^1-Isocyclicsulfanilamides: carboxy derivatives



R^1	$R^{1'}$	ACTIVITY	REFERENCES
2-$(HOOC)C_6H_4$—	H	+++, ±	(35, 54, 91, 100)
2-$(NaOOC)C_6H_4$—	H	++, 0	(42, 102, 121)
2-$(C_2H_5OOC)C_6H_4$—	H	0	(42)
3-$(HOOC)C_6H_4$—	H	+, ±, 0	(35, 91, 102, 121, 100)
4-$(HOOC)C_6H_4$—	H	+, ++, 0	(9, 11, 35, 54, 100, 102, 121, 165)
4-$(NH_2OC)C_6H_4$—	H		(107)
2-HOOC-4-ClC_6H_3—	H		(28, 29, 91)
3-$(HOOCCH{=}CH)C_6H_4$—	H		(65)
4-$(HOOCCH{=}CH)C_6H_4$—	H		(65)
4-HOOC-3-$(HO)C_6H_3$—	H	0	(42, 91)
4-$(HO)C_6H_4CH_2(HOOC)CH$—	H		(136)

(3) N^1-Isocyclicsulfanilamides: carboxy derivatives (see table 5)

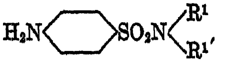
The sulfanilamidobenzoic acids have given variable results with different investigators, probably because of variations in dosage, since these compounds may be absorbed and excreted rapidly. The 2-sulfanilamidobenzoic acid seems slightly more active than the 3- and 4-isomers. All are of low activity against pneumococci (102).

(4) *N*¹-Isocyclicsulfanilamides: sulfo derivatives (see table 6)

The above remarks on the corresponding carboxy derivatives also apply here. It is difficult to maintain adequate blood levels of sodium *N*-sulfanilylsulfanilate. This may partly explain the controversial question of its effectiveness in dog distemper (46, 126). It is reported to be fairly effective in lymphogranuloma venereum infections (73).

TABLE 6

N¹-Isocyclicsulfanilamides: sulfo derivatives



R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
2-$(HO_3S)C_6H_4$—	H	++, 0	(23, 35, 54)
2-HO_3S-4-FC_6H_3—	H	0	(177)
2-HO_3S-4-ClC_6H_3—	H	0	(177)
3-$(HO_3S)C_6H_4$—	H	+, ±	(35, 54, 91)
3-$(NH_2O_2S)C_6H_4$—	H	++, +	(37, 54)
3-HO_3S-4-FC_6H_3—	H	0	(177)
3-HO_3S-4-ClC_6H_3—	H	0	(177)
4-$(HO_3S)C_6H_4$—	H	±	(35, 65, 91, 100)
4-$(HO_3S)C_6H_4$—	C_2H_5—	0	(42)
4-$(NaO_3S)C_6H_4$—	H	±, 0	(35, 100, 102, 121, 127, 158)
4-HO_3S-2-ClC_6H_3—	H	0	(42)
4-NaO_3S-2,5-$Cl_2C_6H_2$—	H	0	(42)
4-HO_3S-2-$(CH_3)C_6H_3$—	H	+, 0	(35, 91, 121)
5-HO_3S-2-$(CH_3)C_6H_3$—	H		(91)
4-HO_3S-3-$(CH_3)C_6H_3$—	H	0	(35, 91)
2-HO_3S-4-$(CH_3)C_6H_3$—	H	0	(23, 35)
4-HO_3S-2,5-$(CH_3)_2C_6H_2$—	H	0	(35)
1-NaO_3S-5-$C_{10}H_6$—	H	+	(35)
4-NaO_3S-1-$C_{10}H_6$—	H	++, 0	(54, 35, 91)
6-HO_3S-2-$C_{10}H_6$—	H		(35)
3,5-$(HO_3S)_2C_6H_3$—	H	0	(37)
3,6-$(HO_3S)_2$-1-$C_{10}H_5$—	H		(91)
3,8-$(HO_3S)_2$-1-$C_{10}H_5$—	H		(91)
4,8-$(NaO_3S)_2$-1-$C_{10}H_5$—	H	0	(121)
5-NaO_3S-2-$(HO)C_6H_3$—	H	0	(121)
3-HO_3S-4-$(C_2H_5O)C_6H_3$—	H	0	(35)
7-HO_3S-5-HO-2-$C_{10}H_5$—	H		(91)
6-HO_3S-8-HO-2-$C_{10}H_5$—	H		(91)

Addition of a third group to the *N*¹-aryl, when this is halogen, alkyl, oxy, or sulfo, destroys the activity.

(5) N^1-Isocyclicsulfanilamides: amino derivatives (see table 7)

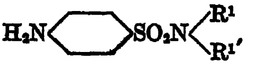
The N^1-aminophenylsulfanilamides have been extensively studied abroad. Whitby (11) reported them to be somewhat inferior to sulfanilamide in antistreptococcic effect, but equal against meningococci and superior against pneumococci. Others have given conflicting evaluations. N^1-(4-Aminophenyl)sulfanilamide as its tartrate was studied clinically in Europe, but withdrawn because it gave a high incidence of peripheral neuritis.

The series of N^1-(4-benzilidineaminophenyl)sulfanilamides (102) is interesting because of the variation in activity with different substituted benzilidine groups. If these anils are hydrolyzed in the body, the resulting activities might be expected to be that of the parent N^1-(4-aminophenyl)sulfanilamide except as modified by rates of absorption and hydrolysis.

The *bis*-sulfanilamidobenzenesulfonic acids and their salts are of passing interest, since they were found to be active when given parenterally but inactive *per os* (35, 54). In spite of high water-solubility, these compounds are not absorbed from the intestinal tract. This is again an illustration of the importance of studying blood levels of the drug in experimental therapy.

(6) N^1-Isocyclicsulfanilamides: miscellaneous derivatives

The three derivatives listed, all arsonic acid derivatives, are apparently inactive against streptococci.



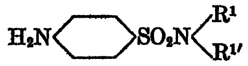
R^1	$R^{1'}$	ACTIVITY	REFERENCES
4-[$(HO)_2OAs$]C_6H_4—	H	0	(178)
4-($NaHO_3As$)C_6H_4—	H	±	(121)
3-[4-[$(HO)_2OAs$]$C_6H_4N{=}N$]-4-$(HO)C_6H_3CH_2(HOOC)CH$—	H		(136)

(D) *Heterocyclic substituents*

This class of derivatives is being both extensively and intensively studied. The spectacular success of sulfapyridine against pneumonia has resulted in a gold-rush to the new field and new strikes are being made in quick succession. Two veins of the original lode have been uncovered in sulfathiazole (2-sulfanilamidothiazole) and sulfadiazine (2-sulfanilamidopyrimidine), which may prove to be of equal or greater importance. These

TABLE 7

N^1*-Isocyclicsulfanilamides: amino derivatives*



R^1	R$^{1'}$	ACTIVITY	REFERENCES
2-(NH$_2$)C$_6$H$_4$—	H	±	(76, 121, 187)
3-(NH$_2$)C$_6$H$_4$—	H	+	(24, 76, 121, 187, 188)
4-(NH$_2$)C$_6$H$_4$—	H	+++, ++, ±	(119, 121, 127, 131, 187, 188)
4-(CH$_3$NH)C$_6$H$_4$—	H		(76)
4-[(CH$_3$)$_2$N]C$_6$H$_4$—	H		(65, 76, 84, 131)
4-[(C$_2$H$_5$)$_2$N]C$_6$H$_4$—	H		(76)
4-(C$_6$H$_5$NH)C$_6$H$_4$—	H		(84)
4-(C$_6$H$_5$CH=N)C$_6$H$_4$—	H	+++	(102)
4-[4′-(NO$_2$)C$_6$H$_4$CH=N]C$_6$H$_4$—	H	+	(102)
4-[4′-(CH$_3$O)C$_6$H$_4$CH=N]C$_6$H$_4$—	H	++	(102)
4-[4′-[(CH$_3$)$_2$N]C$_6$H$_4$CH=N]C$_6$H$_4$—	H	++	(102)
3-CH$_3$-4-(NH$_2$)C$_6$H$_3$—	H		(84)
2-CH$_3$-5-(NH$_2$)C$_6$H$_3$—	H		(76)
5-CH$_3$-2-(NH$_2$)C$_6$H$_3$—	H		(76)
2,3-(CH$_3$)$_2$-4-(NH$_2$)C$_6$H$_2$—	H		(76)
2,4-(NH$_2$)$_2$C$_6$H$_3$—	H		(84)
3,4-(NH$_2$)$_2$C$_6$H$_3$—	H		(131)
4-[4′-(NH$_2$)C$_6$H$_4$NH]C$_6$H$_4$—	H		(131)
4-HO-3-(NH$_2$)C$_6$H$_3$—	H	0	(121)
3-HO-4-(NH$_2$)C$_6$H$_3$—			(84, 131)
2-NH$_2$-5-(NaO$_3$S)C$_6$H$_3$—	H	0	(35)
2-[4′-(NH$_2$)C$_6$H$_4$SO$_2$NH]C$_6$H$_4$—	H	0	(42)

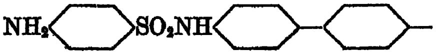
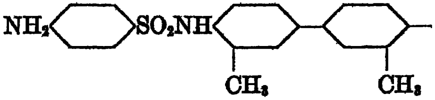
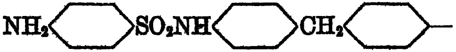
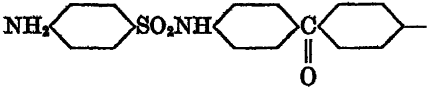
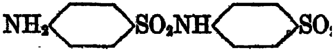
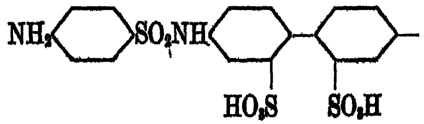
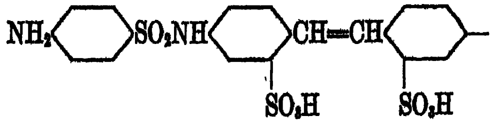
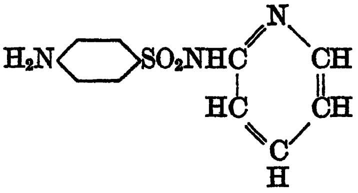
3- $(NH_2)C_6H_4SO_2NH]C_6H_4$—	H	±	(35, 83)
4- $(NH_2)C_6H_4SO_2NH]C_6H_4$—	H	++	(35,
3, 4′-$(NH_2)C_6H_4SO_2NH]_2C_6H_3$—	H	0	(42)
4- $(NH_2)C_6H_4SO_2NH]$-2,5-$(CH_3O)_2C_6H_2$—	H		(83)
4- $(NH_2)C_6H_4SO_2NH]$-2-CH_3-5-$(CH_3O)C_6H_2$	H		(83)
4- $(NH_2)C_6H_4SO_2NH]$-1-$C_{10}H_6$—	H		(83)
5- $(NH_2)C_6H_4SO_2NH]$-1-$C_{10}H_6$—	H		(83)
8- $(NH_2)C_6H_4SO_2NH]$-1-$C_{10}H_6$—	H		(83)
6- $(NH_2)C_6H_4SO_2NH]$-2-$C_{10}H_6$—	H		(83)
	H		(83)
	H		(83)
	H		(83)
	H		(83)
	H	±	
2-[4′-$(NH_2)C_6H_4SO_2NH]$-5-$(NaO_3S)C_6H_3$—	H	±	
3-[4′-$(NH_2)C_6H_4SO_2NH]$-4-$(NaO_3S)C_6H_3$—	H	+++,	54)
5-[4′-$(NH_2)C_6H_4SO_2NH]$-2-NaO_3S-4-$(CH_3)C_6H_2$—	H	0	
4-[4′-$(NH_2)C_6H_4SO_2NH]$-2-$(HO_3S)C_6H_3$—	H	+++,	

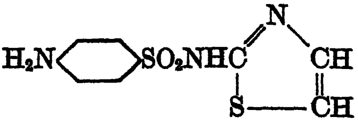
TABLE 7—*Concluded*

R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
	H	0	(35)
	H	0	(35)
$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CH_2\text{—}$	H	0	(40)
$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CH_2\text{—}$	$HOCH_2CH_2\text{—}$		(40)
$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CH_2\text{—}$	$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CH_2\text{—}$	0	(40)
$4\text{-}(NH_2)C_6H_4SO_2NHCH_2CHOHCH_2\text{—}$	H	±, −	(40, 179)
$2,6\text{-}(HO_3S)_2\text{-}4\text{-}(NH_2)C_6H_2\text{—}$	H		(91)
$4\text{-}[4'\text{-}(NH_2)C_6H_4SO_2]C_6H_4\text{—}$	H	±	(54, 161)
$4\text{-}[4'\text{-}(4''\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4O]C_6H_4\text{—}$	H		(83)
$4\text{-}[4'\text{-}(4''\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4S]C_6H_4\text{—}$	H		(83)
$4\text{-}[4'\text{-}(4''\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4SO_2]C_6H_4\text{—}$	H		(62, 83)
$4\text{-}[4'\text{-}(4''\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4NH]C_6H_4\text{—}$	H		(83)
$4\text{-}[[4\text{-}(4'\text{-}(NH_2)C_6H_4SO_2NH)C_6H_4]_2C(OH)]C_6H_4\text{—}$	H	0	(42, 54)

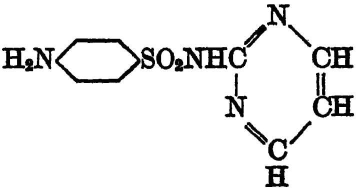
compounds are all isosteric, as may be seen by an inspection of their structural formulas.



Sulfapyridine



Sulfathiazole



Sulfadiazine

The number of compounds so far disclosed is remarkable in view of the difficulties in synthesis, both of the amino heterocycles and of their sulfanilyl derivatives. For convenience, these compounds are further subdivided on the basis of the number of nitrogen, oxygen, or sulfur atoms in the heterocyclic system.

(1) N^1-Heterocyclicsulfanilamides: one oxygen or one sulfur atom in the heterocyclic system (see table 8)

Only two N^1-heterocyclic derivatives containing one oxygen atom in the heterocyclic system have been disclosed, and both are inactive. In these derivatives of mono- and di-furfurylamine the amido group is not attached to the ring but to a side chain, so that these derivatives are not isosteric with sulfapyridine.

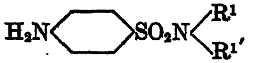
(2) N^1-Heterocyclicsulfanilamides: one nitrogen atom in the heterocyclic system

A great many substituted 2- and 3-sulfanilamidopyridines have been made, but of the 4-sulfanilamidopyridines only the parent compound has so far been disclosed (see tables 9, 10, 11). Difficulties in the synthesis of 4-substituted pyridines is the obvious reason.

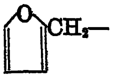
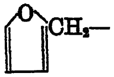
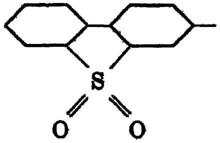
There was no significant difference in activity between 2- and 3-sulfanilamidopyridine on either streptococci or pneumococci (160). Remarkable differences developed in the study of their substitution products, however. In 2-sulfanilamidopyridine, substitution of halogen in the 5-position destroyed the activity, while nitro or amino groups in the 5-position gave slightly enhanced activity against streptococci and slightly less activity against pneumococci. When the positions of the groups were reversed, i.e., substituents introduced in the 2-position in 5-sulfanilamidopyridine, the halogen derivatives were now active and the nitro and amino derivatives inactive! Blood level studies showed no significant differences between active and inactive compounds, so that the difference in activity must be explained by some inherent difference in the compounds themselves.

TABLE 8

N^1-Heterocyclicsulfanilamides: one oxygen or one sulfur atom in the heterocyclic system



$H_2NC_6H_4SO_2N(R^1)(R^{1\prime})$

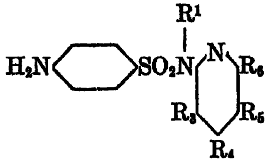
R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
	H		(42, 54)
	CH_3		(40)
4-$(NH_2)C_6H_4SO_2NH$-			(83)

Theories of the mechanism of the action of sulfanilamide derivatives might well be tested against such pairs of compounds. It is difficult to understand in terms of a postulated *in vivo* oxidation of the amino group to hydroxylamine as the active form, the profound influence of isomerism in an N^1-substituent. One fears that the architecture of new chemotherapeutic agents will continue to be an empirical science for some time to come!

In the sulfanilamidoquinoline series (see tables 12 and 13), few activities have been disclosed. However, there seems to be a marked drop in activity and increase in toxicity as compared with the corresponding sulfanilamidopyridines (54). The corresponding isoquinoline derivative, though inactive, was less toxic.

TABLE 9

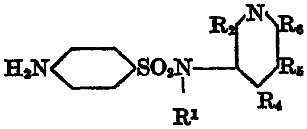
2-Sulfanilamidopyridines



				+++, ++	39, 6 102, 132, 160, 83, 187,
Na—				+++	129,
CH_3—					132)
C_6H_5CH					132)
		Br—		0	160)
		I—		0	132, 60)
		NO_2—		+++	160)
			CH		132, 83)
	C_2H_5O—			+	160)
	HOOC—				132)
		HO			132
		NH		+++	160
			NH_2—	+++	59, 83
		$NH_2)C_6H$		+	160
			-$(NH_2)C_6H_4SO_2NH$—		132

TABLE 10

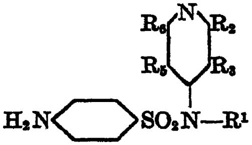
3-Sulfanilamidopyridines



R^1	R_2	R_4	R_5	R_6	ACTIVITY	REFERENCES
					+++	(54, 160, 190)
				Cl—	+++	(160)
				Br—	+++	(160)
				HO—	0	(160)
				C_2H_5O—	+	(160)
				NH_2—	0	(160, 190)

TABLE 11

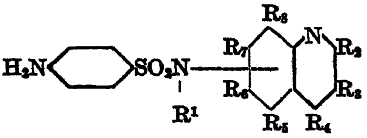
4-Sulfanilamidopyridines



R^1	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
						(132, 102)

TABLE 12

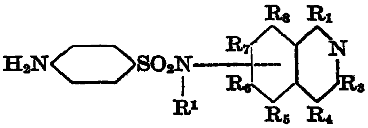
x-Sulfanilamidoquinolines



R^1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	ACTIVITY	REFERENCES
	x							±	(42, 54, 132, 183)
		x							(190)
				x					(14, 190)
					x				(14, 132, 190)
						x			(14)
							x	+	(14, 29, 190)
	CH_3—				x				(132)
	C_6H_5—		x						(8)
				x			CH_3O—		(132)
					CH_3O—			+	(29, 45)
	HO—		CH_3—				x		(132)
	C_6H_5—		x		CH_3O—				(8)

TABLE 13

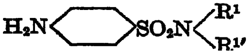
x-Sulfanilamidoisoquinolines

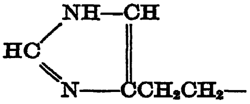
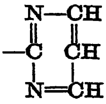
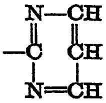
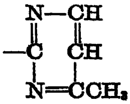
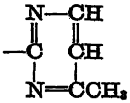
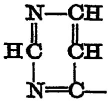
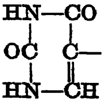
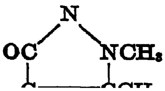


R^1	R_1	R_3	R_4	R_5	R_6	R_7	R_8	ACTIVITY	REFERENCES
	x							0	(42, 54, 132)

TABLE 14

N^1-Heterocyclicsulfanilamides: two or more nitrogen atoms in the heterocyclic system



R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
	H	0	(42, 54)
	H	+++	(159)
	Na—	+++	(159)
	H	+++	(159)
	Na—	+++	(159)
	H	0	(159)
	H	0	(159)
	H	0	(159)

(3) N^1-Heterocyclicsulfanilamides: two or more nitrogen atoms in the heterocyclic system (see table 14)

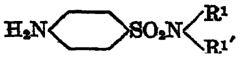
2-Sulfanilamidopyrimidine ("sulfadiazine") (159) has shown several important advantages over sulfapyridine in preliminary studies. It is very readily absorbed, so that adequate blood levels can be maintained at lower dosage levels. Since 2-(N^4-acetylsulfanilamido)pyrimidine is slightly more soluble than 2-sulfanilamidopyrimidine, danger of kidney damage should be less than for sulfapyridine and sulfathiazole, where the reverse solubility relationship holds. Another favorable point is that in 10 per cent aqueous solution the pH of the sodium salt is 9.6 to 9.7, as against pH values of approximately 10 for sodium sulfathiazole and 11 for sodium sulfapyridine.

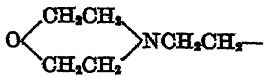
2-Sulfanilamido-4-methylpyrimidine, "sulfamethyldiazine," appears equal to the parent compound in activity on both pneumococci and streptococci. 4-Sulfanilamidopyrimidine is apparently completely inactive, as is 5-sulfanilamidouracil.

While not listed, it might be noted that 5-(*p*-nitrobenzenesulfonyl)tetrazole was synthesized, but could not be reduced to the corresponding 5-sulfanilamidotetrazole without rupture of the tetrazole ring, giving rise to sulfanilylguanidine (159). The nitro group was apparently reduced in the body, since a diazotizable amine could be measured in the blood. The compound was inactive, while the guanidine derivative, which gave more rapid absorption and elimination, showed slight activity. This suggested that the tetrazole ring was not broken down *in vivo* (159).

(4) N^1-Heterocyclicsulfanilamides: one nitrogen atom and one oxygen (or sulfur) atom in the heterocyclic system

Only one derivative of the type containing one nitrogen atom and one sulfur atom in the heterocyclic system has been disclosed and it was found to be inactive; however, the point of attachment was on a side chain rather than to the ring.

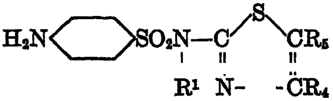


R^1	$R^{1'}$	ACTIVITY	REFERENCE
	H	0	(40)

The sulfanilamidothiazoles have been well explored chemically (see tables 15 and 16). 2-Sulfanilamidothiazole ("sulfathiazole") and 2-sulfanilamido-4-methylthiazole ("sulfamethylthiazole") are very active

TABLE 15

2-Sulfanilamidothiazoles

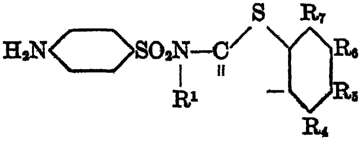


R^1	R_4	R_5	ACTIVITY	REFERENCES
		*	++	(6, 33, 59, 121, 124, 127, 133, 159, 174, 185)
Na—			++	(124, 185)
C_2H_5—				(133)
	CH_3—	†	++	(6, 33, 59, 124, 127, 133, 159, 174, 183)
CH_3—	CH_3—		±	(133, 174)
$C_6H_5CH_2$—	CH_3—			(133)
		CH_3—		(133)
C_2H_5—		CH_3—		(133)
	C_2H_5—			(124)
		C_2H_5—		(133)
	C_6H_5—	‡	+	(6, 133, 174)
	4-$(C_6H_5)C_6H_4$—		0	(159)
	CH_3—	CH_3—		(133)
	CH_3—	C_6H_5—		(133)
	CH_3—	$HOCH_2CH_2$—		(133)
	CH_3—	HOOC—		(133)
	CH_3—	C_2H_5OOC—	±	(133, 174)

* Sulfathiazole. † Sulfamethylthiazole. ‡ Sulfaphenylthiazole.

TABLE 16

2-Sulfanilamidobenzothiazoles

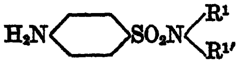


R^1	R_4	R_5	R_6	R_7	ACTIVITY	REFERENCES
					0	(133, 159)
C_2H_5—						(133)
			NO_2—			(133)
			CH_3—			(133)
			C_2H_5O—			(133)
		NH_2—				(133)
		CH_3CONH—				(133)

against both streptococci and pneumococci, and in addition are effective against staphylococci. Sulfathiazole is more regularly absorbed than sulfapyridine and has had wide clinical study against pneumonia and staphylococcal septicemias, with generally favorable results. Sulfamethylthiazole was withdrawn from clinical study because about 2 per cent of the patients treated with it developed peripheral neuritis of more or less serious character. Sulfathiazole has not shown this disadvantage, although kidney damage is possible and must be carefully watched for by the clinicians.

TABLE 17

N^1-*Heterocyclicsulfanilamides: miscellaneous derivatives*



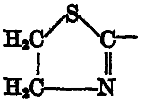
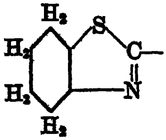
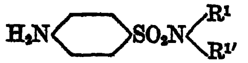
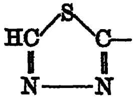
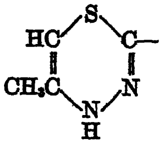
R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	+	(174)
	H	±	(60, 174)

TABLE 18

N^1-*Heterocyclicsulfanilamides: two nitrogen atoms and one sulfur atom in the heterocyclic system*



R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	±	(159)
	H	+	(60)

Some miscellaneous heterocyclic derivatives containing one nitrogen atom and one sulfur atom in the heterocyclic system are given in table 17.

(5) N^1-Heterocyclicsulfanilamides: two nitrogen atoms and one oxygen (or sulfur) atom in the heterocyclic system (see table 18)

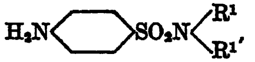
2-Sulfanilamidothiodiazole, while practically inactive against streptococci, was active against pneumococci (159). This is the reverse of usual findings.

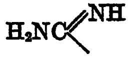
(6) N^1-Heterocyclicsulfanilamides: N^1-nitrogen in the heterocyclic system

Not many derivatives have been made of this type, and they appear to be of low activity (see table 19).

(E) Acyl substituents

This series of derivatives has been well explored chemically, with the exception of derivatives of carbonic acid, of which only the guanidine derivative has been described, and it was only slightly active.



R¹	R¹′	ACTIVITY	REFERENCE
	H	±	(159)

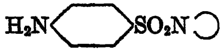
The series of straight-chain acyclic-acyl derivatives is almost complete to eighteen carbon atoms (see table 20). The first member, N^1-acetylsulfanilamide, while only moderately active against streptococci, has been widely sold outside of this country under the name "Albucid" for use in the treatment of gonorrhea. Claims are made that high dosage can be maintained without as much danger of toxic reactions as accompanies the use of sulfanilamide, sulfapyridine, and Uleron.

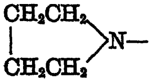
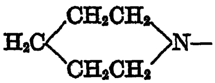
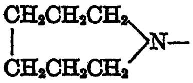
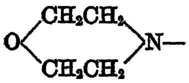
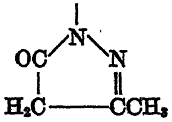
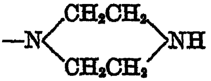
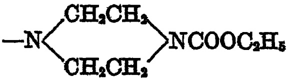
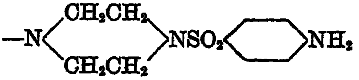
According to Henderson (75), 39 per cent of N^1-acetylsulfanilamide is hydrolyzed in the human body to sulfanilamide and part of this is converted to N^4-acetylsulfanilamide. Examination of the urine shows that of the total urinary sulfanilamides, 61 per cent is unchanged N^1-acetylsulfanilamide, 28.8 per cent N^4-acetylsulfanilamide, and 10.2 per cent sulfanilamide.

The higher members of the straight-chain series apparently go through peak activity in N^1-butyrylsulfanilamide and N^1-dodecanoylsulfanilamide (55). To obtain adequate absorption of the long-chain compounds, it was found necessary to administer them with oils or fats. Sulfanilamide itself is also better absorbed when given with oils. When N^1-butyrylsulfanilamide and N^1-dodecanoylsulfanilamide are administered with oil and compared with sulfanilamide in oil for antistreptococcic effect, they are about equal on an equal weight dosage, but definitely superior on an equimolecular dosage. This is of interest, since blood studies indicate that these compounds are largely hydrolyzed to sulfanilamide during some stage of absorption. However, no breakdown could be detected in the intestine.

TABLE 19

N^1-Heterocyclicsulfanilamides: N^1-nitrogen in the heterocyclic system

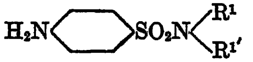


	ACTIVITY	REFERENCES
		(88)
	±	(68, 70, 86, 87, 88)
	0	(179)
	±	(2, 42, 121)
	+	(159)
	0	(33, 98, 127)
		(98)
		(98)

The marked drop in activity between the straight-chain and branched-chain derivatives, e.g., N^1-butyrylsulfanilamide and N^1-isobutyrylsulfanilamide, is curious if activities can be explained on the basis of hydrolysis to sulfanilamide. More work is evidently needed to settle such questions.

TABLE 20

N^1-Acyclic-acylsulfanilamides



R^1	$R^{1'}$	ACTIVITY	REFERENCES
$CH_3CO—$	H*	+	(38, 47, 55)
$CH_3CO—$	$Na—$		(38)
$CH_3CO—$	$NH_4—$		(38)
$CH_3CO—$	$—NH_2(C_2H_5)_2$		(38)
$CH_3CH_2CO—$	H	++	(38, 55)
$CH_3(CH_2)_2CO—$	H	+++	(38, 55)
$(CH_3)_2CHCO—$	H	±	(38, 54)
$CH_3(CH_2)_3CO—$	H	++	(42, 55)
$(CH_3)_2CHCH_2CO—$	H	±	(38, 54)
$(C_2H_5)_2CHCO—$	H		(38)
$CH_3(CH_2)_4CO—$	H	+	(38, 55)
$CH_3(CH_2)_5CO—$	H	+	(38, 55)
$CH_3(CH_2)_3CH(C_2H_5)CO—$	H		(38)
$CH_3(CH_2)_6CO—$	H	++	(38, 55)
$CH_3(CH_2)_8CO—$	H	++	(38, 55)
$CH_3(CH_2)_9CO—$	H	++	(38, 55)
$CH_3(CH_2)_{10}CO—$	H	+++	(38, 55)
$CH_3(CH_2)_{10}CO—$	$Ag—$		(38)
$CH_3(CH_2)_{10}CO—$	$\frac{1}{2}Hg—$		(38)
$CH_3(CH_2)_{10}CO—$	$\frac{1}{2}Ca—$		(38)
$CH_3(CH_2)_{10}CO—$	$CH_3—$		(38)
$CH_3(CH_2)_{12}CO—$	H	++	(38, 55)
$CH_3(CH_2)_{14}CO—$	H	+	(42, 54)
$CH_3(CH_2)_{16}CO—$	H	+	(38, 55)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO—$	H		(38).

* Albucid.

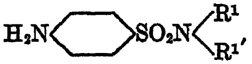
The reported activity of N^1-dodecanoylsulfanilamide (38) against experimental tuberculosis in guinea pigs has not been substantiated by clinical studies.

The N^1-aracylsulfanilamides (see table 21) again show surprising differences in activities.

In the N^1-heterocyclic-acylsulfanilamides (table 22), it is remarkable that N^1-nicotinylsulfanilamide is inactive (54), while N^4-nicotinylsulfanilamide (see III, E (4)) is said to be highly active (43).

TABLE 21

N^1-Isocyclic-acylsulfanilamides



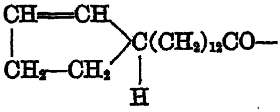
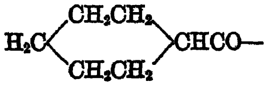
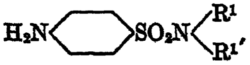
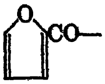
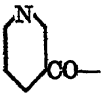
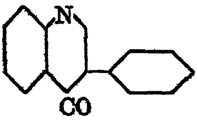
R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
	H	++	(38)
	H	++	(38)
$C_6H_5CO—$	H		(38, 54)
$C_6H_5CH_2CH_2CO—$	H	++	(38, 54)
$C_6H_5CH{=}CHCO—$	H	++	(38, 54)
$C_6H_5CH{=}CHCO—$	Na—	++	(38, 54)
$(C_6H_5)_2CHCO—$	H	±	(38, 54)
$4\text{-}(NO_2)C_6H_4CO—$	H	0	(38, 54)
$C_6H_5CH(OH)CO—$	H	0	(38, 54)
$2\text{-}(HO)C_6H_4CO—$	H	++	(127)
$3\text{-}HO\text{-}2\text{-}C_{10}H_6CO—$	H		(38)
$4\text{-}(HOOC)C_6H_4CO—$	H		(38, 54)
$4\text{-}(NH_2)C_6H_4CO—$	H		(38)
$4\text{-}(NH_2)C_6H_4SO_2NHCO(CH_2)_8CO—$	H		(38)

TABLE 22

N^1-Heterocyclic-acylsulfanilamides



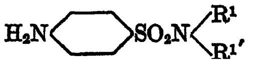
R^1	$R^{1\prime}$	
		(38)
		(38, 54)
		(38, 54)

(*F*) *N^1-Sulfonyl substituents*

The N^1-acyclicsulfonylsulfanilamides (table 23) appear to be completely inactive, as are the N^1-cycloalkanesulfonylsulfanilamides. Wide discrepancies are shown for activities of disulfanilamide (not to be confused with N^4-sulfanilylsulfanilamide, which was first misnamed disulfanilamide) and its N^1-alkyl derivatives. Free disulfanilamide appears not to be absorbed when given *per os* and first results were reported for parenteral administration. Sodium disulfanilamide, on the other hand, is rapidly absorbed and eliminated. The early reports of effectiveness by Climenko (36) have not been confirmed by Feinstone, using a more vigorous test which tends to favor compounds giving sustained blood levels (54).

TABLE 23

N^1-Alkanesulfonylsulfanilamides



R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
$CH_3CH_2SO_2$—	H	0	(41)
$CH_3(CH_2)_3SO_2$—	H	0, ±	(41, 174)
$CH_3(CH_2)_3SO_2$—	Na—	0	(42)
$CH_3(CH_2)_4SO_2$—	H	0, ±	(41, 174)
$CH_3(CH_2)_4SO_2$—	Na—	0	(42)
$CH_3(CH_2)_3CH(C_2H_5)CH_2SO_2$—	H		(41)
$CH_3(CH_2)_{11}SO_2$—	H	0	(41)

The reported moderate effectiveness of sodium disulfanilamide in experimental influenza virus infections (36) was not duplicated with sufficient regularity to be significant.

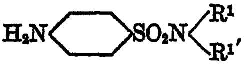
The N^1-isocyclic-sulfonyl derivatives are listed in table 24. No N^1-heterocyclic-sulfonylsulfanilamides have been prepared.

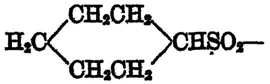
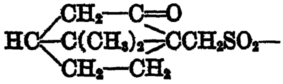
III. N^4-SUBSTITUTED SULFANILAMIDES

Unless the substituting group in the N^4-position is hydrolyzed, reduced, or otherwise removed *in vivo*, it appears that the derivative will have little, if any, activity. That such processes do occur has been amply demonstrated by the finding of a diazotizable amine in the blood after feeding 4-nitro-, hydroxylamino-, azo-, N^4-acyl-, anil and reduced anil, aldehyde-bisulfite, and aldehyde-sulfoxalate sulfanilamides, and by the isolation of sulfanilamide from the urine of animals so treated. It has not been proved that the activities of these compounds are entirely the result of cleavage with liberation of sulfanilamide, but there is much which points to such a mechanism. It is quite possible that the superior properties claimed for certain derivatives of this type are a result of slow cleavage with prolonged maintenance of therapeutic blood levels of sulfanilamide, or whatever active form may be derived *in vivo* from sulfanilamide.

TABLE 24

N^1-isocyclic-sulfonylsulfanilamides



R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
	H	0	(41, 54)
4-$(NO_2)C_6H_4SO_2$—	H		(42)
$C_6H_5CH_2SO_2$—	H	±	(41, 174)
4-$(NO_2)C_6H_4CH_2SO_2$—	H		(42)
4-$(HO)C_6H_4SO_3$	H	±	(42)
	H	0	(41, 54)
4-$(NH_2)C_6H_4SO_2$—	H	+++, +, 0	(22, 36, 54)
4-$(NH_2)C_6H_4SO_2$—	Li—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	Na—	+++, 0	(22, 36, 54)
4-$(NH_2)C_6H_4SO_2$—	$\frac{1}{2}$Mg—	++	(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$\frac{1}{2}$Ca—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$\frac{1}{2}$Ba—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$\frac{1}{2}$Cu—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$\frac{1}{2}$Ni—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	Ag—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$\frac{1}{2}$Pb—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$\frac{1}{2}$Hg—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$\frac{1}{2}$Zn—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	NH_4—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$(C_2H_5)_2NH_2$—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$C_5H_{11}NH_3$—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	$(HOCH_2CH_2)_3NH$—		(22, 36)
4-$(NH_2)C_6H_4SO_2$—	CH_3—	+++, 0	(22, 36, 54)
4-$(NH_2)C_6H_4SO_2$—	C_2H_5—	+++, 0	(22, 36, 54)
4-$(NH_2)C_6H_4SO_2$—	$C_{12}H_{25}$—	0	(42, 54)
4-$(NH_2)C_6H_4CH_2SO_2$—	H		(42)

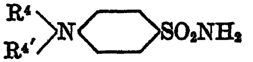
(*A*) *Inorganic substituents*

4-Hydroxylaminobenzenesulfonamide (N^4-hydroxysulfanilamide) (see table 25) was prepared by Mayer and Oechslin (134), who stated that it was one hundred times as active *in vitro* as sulfanilamide and suggested that the activity of sulfanilamide might be the result of an *in vivo* oxidation to the hydroxylamine.

Bratton, White, and Marshall (16) have more fully described the preparation and properties of the compound, and state that it is not more than ten times as active *in vitro*. When injected into dogs, it appeared to be completely converted to sulfanilamide within 5 min.

TABLE 25

Sulfanilamides containing inorganic substituents in the N^4-position



R^4	$R^{4'}$	ACTIVITY	REFERENCES
HO—	H	++, +	(16, 134, 162)
NH_2—	H	0	(20, 134)
H_2O_2P—	H	±	(179)

Much current research on the mechanism of the action of sulfanilamide has centered on this compound. The subject is highly controversial and the author does not feel qualified to review the work critically.

(*B*) *Acyclic substituents*

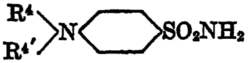
With the exception of the N^4-formaldehyde-bisulfite, N^4-formaldehyde-sulfoxalate, and N^4-glucose-bisulfite derivatives, all of which are probably hydrolyzed to sulfanilamide *in vivo*, these derivatives have little or no activity (see table 26).

(*C*) *Isocyclic substituents*

The only true N^4-arylsulfanilamides were reported without pharmacological data. Most of the other derivatives (see table 27) have been obtained by the reduction of the corresponding anils. With the exception of N^4-(4′-nitrobenzyl)sulfanilamide, these are of relatively low activity and apparently owe their activity to cleavage to sulfanilamide *in vivo* (144). The high activity reported for the 4′-nitrobenzyl derivative is difficult to explain on this basis. Possibly it gives a double action on cleavage, since Rosenthal (197) has reported activity for *p*-nitrotoluene and *p*-nitrobenzoic acid. Further investigations of the products present in the blood stream may shed light on this anomaly and will be awaited with interest.

TABLE 26

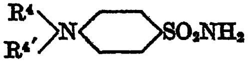
N^4-Acyclicsulfanilamides



R^4	$R^{4'}$	ACTIVITY	REFERENCES
CH_3—	H	+	(120)
C_5H_{11}—	H	±	(32)
$HOCH_2CH_2$—	H	±, −	(155, 179)
$HOCH_2(CHOH)_4CH_2$—	H		(52)
$HOOCCH_2$—	H	±	(27, 52, 57, 89, 95, 96, 155, 181)
$HOOCCH_2$—	ON—	±	(57)
NH_2OCCH_2—	H	±	(89, 181, 184)
$C_2H_5OOCCH_2$—	H		(89)
$HOOCCH_2CH_2$—	H	+	(155)
$HOOC(CH_3)CH$—	H		(52)
$HOOCCH_2(HOOC)CH$—	H		(52)
NaO_2SCH_2—	H	++, +	(10, 57, 89, 96, 121, 163)
NaO_3SCH_2—	H	++	(57, 67, 96, 173)
$HOCH_2(CHOH)_4\overset{\vert}{C}HSO_3Na$	H	+++	(178)

TABLE 27

N^4-Isocyclicsulfanilamides



R^4	$R^{4'}$	ACTIVITY	REFERENCES
C_6H_5—	H		(90)
$C_6H_5CH_2$—	H*	+	(67, 70, 72, 135, 163, 172, 188)
4-$(NO_2)C_6H_4CH_2$—	H	+++	(77, 135, 162, 178)
$C_6H_5(CH_2)_3$—	H		(90)
2-$(HO)C_6H_4CH_2$—	H	±	(67, 90)
4-$(HO)C_6H_4CH_2$—	H	±	(67, 90)
2,4-$(HO)_2C_6H_3CH_2$—	H	±	(67)
2,4,6-$(HO)_3C_6H_2CH_2$—	H	±	(67)
3-Cl-4-$(HOOC)C_6H_3$—	H		(7)
3-$(NaO_3S)C_6H_4CH_2$—	H		(172)
$C_6H_5(NaO_3S)CH$—	H		(173)
$C_6H_5CH_2(NaO_3S)CH$—	H		(173)
$C_6H_5CH(SO_3Na)CH_2(NaO_3S)CH$—	H†	+	(173, 188)
4-$(NH_2)C_6H_4CH_2$—	H		(77)
4-$[(CH_3)_2NH]C_6H_4CH_2$—	H		(77)
C_6H_5NH—	H		(91)
4-$(NH_2SO_2)C_6H_4NH$—	H	0	(134)

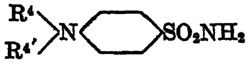
* Septazine. † Soluseptazine.

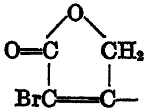
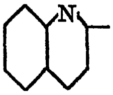
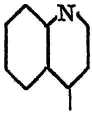
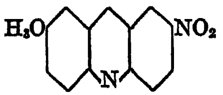
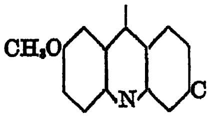
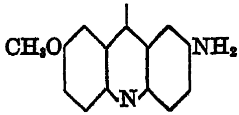
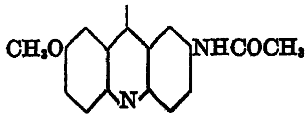
(*D*) *Heterocyclic substituents* (*see tables 28 and 29*)

These compounds appear to be inactive (with the exception of N^4-*α*-bromotetronylsulfanilamide, which behaves as an N^4-acylsulfanilamide and is probably cleaved *in vivo*). This supports the hypothesis of the

TABLE 28

N^4-Heterocyclicsulfanilamides: N^4-nitrogen not in the heterocyclic system

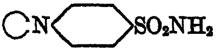


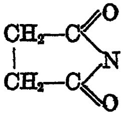
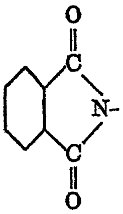
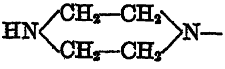
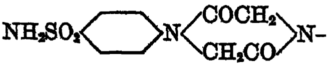
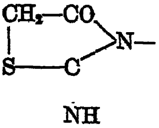
R^4	$R^{4'}$		
	H	++	(105)
	H		(69)
			(14, 69)
	H		(8, 14)
			(49)
	H		(182)
	H		(49)
	H		(49)

necessity of a potentially free amino group in sulfanilamide derivatives, since the probability of cleavage at such a linkage is remote. The acridine derivatives were synthesized for probable use against malaria, but with what success is not known.

TABLE 29

N^4-Heterocyclicsulfanilamides: N^4-nitrogen in the heterocyclic system



	REFERENCES
	(143)
	(60)
	(99)
	(1)
	(1)

(*E*) *Acyl substituents*

(1) N^4 substituents derived from carbonic acid

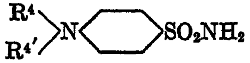
The sulfanilamides containing, in the N^4-position, groups derived from carbonic acid (see table 30) do not appear to be active, with the exception of the guanidine derivative (19), which is said to be equal to sulfanilamide in activity and toxicity. It has not been disclosed whether this compound is cleaved to sulfanilamide on absorption, but it is of interest that it should be active while the corresponding urea derivative is inactive.

(2) N^4-Acyclic-acylsulfanilamides (see table 31)

N^4-Acetylsulfanilamide is the conjugated form of sulfanilamide produced *in vivo* by the administration of sulfanilamide. It has little or no activity. Ockerblad and Carlson (197) have shown that a small amount of sulfanilamide is present in the blood of dogs fed N^4-acetylsulfanilamide, thus indicating that conjugation is a reversible process. Some of the higher straight-chain acyl derivatives show appreciable activity. The activity passes through a maximum for N^4-valeryl- and N^4-caproyl-sulfanilamides (143). This activity is probably the result of hydrolysis to sulfanilamide. As in the N^1-acyl series, the corresponding branched chain N^4-acylsulfanilamides are inactive or nearly so. This is remarkable and needs study.

TABLE 30

Sulfanilamides containing N^4 substituents derived from carbonic acid



R⁴	R⁴'	ACTIVITY	REFERENCES
C_2H_5OCO—	H	+	(2, 61, 90, 181)
$C_{12}H_{25}OCO$—	H		(123)
$(CH_3)_3N(Cl)CH_2CH_2OCO$—	H		(3)
NH_2CO—	H	0	(34, 90, 100, 112)
$CH_3CONHCO$—	H	0	(34)
4-$(NH_2SO_2)C_6H_4NHCO$—	H	±	(61, 79, 181, 186)
$NH_2C({=}NH)$—	H	++	(19)
$NH_2C({=}S)$—	H	−	(179)
$CH_2{=}CHCH_2NHC({=}S)$—	H		(65)
4-$(NH_2SO_2)C_6H_4NHC({=}S)$—	H		(186)

(3) N^4-Isocyclic-acylsulfanilamides (see table 32)

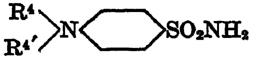
Aside from three inactive derivatives, nothing on the activities of the members of this series has been published. The lack of activity would suggest that experimental animals are unable to hydrolyze aracylamine linkages.

(4) N^4-Heterocyclic-acylsulfanilamides (see table 33)

Three of these derivatives, N^4-(5-pyrrolidone-2-carbonyl)sulfanilamide, N^4-nicotinylsulfanilamide, and the sodium salt of N^4-quinolinylsulfanilamide, are said to be at least as active as sulfanilamide. If the activity is the result of cleavage to sulfanilamide, it remains a mystery why N^4-nicotinylsulfanilamide is cleaved while the isosteric N^4-benzoylsulfanil-

TABLE 31

N^4-Acyclic-acylsulfanilamides



R^4	$R^{4\prime}$	ACTIVITY	REFERENCES
HCO—	H	+	(61, 181)
CH_3CO—	H	±	(20, 61, 181)
CH_3CO—	HO—	0	(16, 162)
CH_3CO—	CH_3—	±	(76, 181)
CH_3CH_2CO—	H	+	(2, 143)
$CH_3(CH_2)_2CO$—	H	+, ±	(2, 143)
$(CH_3)_2CHCO$—	H	±	(2, 84, 132)
$CH_3(CH_2)_3CO$—	H	++, +	(2, 84, 121, 143)
$(CH_3)_2CHCH_2CO$—	H	±	(84, 143)
$CH_3(CH_2)_4CO$—	H	++	(84, 102, 143)
$(CH_3)_2CHCH_2CH_2CO$—	H	0	(84, 143)
$CH_3(CH_2)_5CO$—	H	±	(84, 143)
$CH_3(CH_2)_6CO$—	H	±	(84, 143)
$CH_3(CH_2)_8CO$—	H		(84)
$CH_3(CH_2)_{10}CO$—	H	0	(84, 143)
$CH_3(CH_2)_{12}CO$—	H		(84)
$CH_3(CH_2)_{14}CO$—	H		(84)
$CH_3(CH_2)_{16}CO$—	H		(84)
$CH_3(CH_2)_{20}CO$—	H		(84)
$CH_3CH{=}CH(CH_2)_7CO$—	H		(84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO$—	H		(84)
cis-$CH_3(CH_2)_7CH{=}CH(CH_2)_{11}CO$—	H		(84)
$ClCH_2CO$—	H		(90, 94, 154)
$ClCH_2CH_2CO$—	H		(90)
$(C_2H_5)_2C(Br)CO$—	H		(90)
$HOCH_2CO$—	H	0	(90, 121, 123)
CH_3COOCH_2CO—	H	0	(121)
$CH_3CHOHCO$—	H	0, +	(1, 90, 121)
$CH_3(CH_3COO)CHCO$—	H	0	(1)
CH_3OCH_2CO—	H		(90)
CH_3OCH_2CO—	C_6H_5—		(90)
$C_2H_5OCH_2CO$—	H		(90)
$C_4H_9OCH_2CO$—	H		(90)
CH_3COCH_2CO—	H		(90)
$HOOC(CH_2)_2CO$—	H		(24, 111, 143, 153, 165)
$NaOOC(CH_2)_2CO$—	H	0	(121)
$NH_2OC(CH_2)_2CO$—	H	0	(1)
$HOOCCH{=}CHCO$—	H		(143)
$NaOOCCH{=}CHCO$—	H	0	(121)
NaO_3SCH_2CO—	H	0	(161, 178)
NH_2CH_2CO—	H		(90, 134, 154)
$C_2H_5NHCH_2CO$—	H		(90)
$C_3H_7NHCH_2CO$—	H		(90)
$C_4H_9NHCH_2CO$—	H		(90)
$(C_2H_5)_2NCH_2CO$—	H		(90)
$CH_2{=}CHCH_2NHCH_2CO$—	H		(90)
$C_4H_9NHCH_2CH_2CO$—	H		(90)
$C_4H_9NHC(C_2H_5)_2CO$—	H		(90)

amide, N^4-furoylsulfanilamide, and N^4-thenoylsulfanilamides are not cleaved, but perhaps the latter three owe their lack of activity to lack of absorption.

(*F*) *Sulfonyl substituents* (*see tables 34, 35, and 36*)

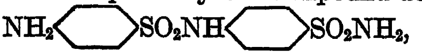
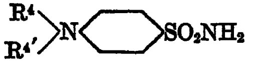
An interesting problem in indexing compounds by the method used herein is posed by the compound designated as N^4-sulfanilylsulfanilamide, , and its N^1 derivatives. On the basis of activity, the parent compound should probably be called N^1-(4-sulfamylphenyl)sulfanilamide, since it is behaving like an N^1-substituted rather than as an N^4-substituted sulfanilamide. However, the nomenclature is so confused on this compound now that it would be inadvisable to complicate the situation further.

TABLE 32

N^4-Isocyclic-acylsulfanilamides



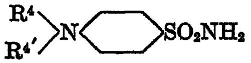
R^4	$R^{4'}$	ACTIVITY	REFERENCES
$C_6H_5CO—$	H	0	(143)
$3\text{-}(NO_2)C_6H_4CO—$	H		(90)
$4\text{-}(NO_2)C_6H_4CO—$	H	±	(162)
$3,5\text{-}(NO_2)_2C_6H_3CO—$	H		(90)
$C_6H_5CH_2CO—$	H		(84)
$C_6H_5CH{=}CHCO—$	H		(84)
$C_6H_5CHOHCO—$	H		(117)
$C_6H_5CH(OOCCH_3)CO—$	H		(117)
$C_6H_5OCH_2CH_2CO—$	H		(90)
$2\text{-}ClC_6H_4OCH_2CH_2CO—$	H		(90)
$2\text{-}[(CH_3)_2CH]\text{-}5\text{-}(CH_3)C_6H_3OCH_2CH_2CO—$	H		(90)
$2\text{-}(HOOC)C_6H_4CO—$	H		(165, 179)
$2\text{-}(NaOOC)C_6H_4CO—$	H	0	(121)
$6\text{-}NO_2\text{-}2\text{-}(HOOC)C_6H_3CO—$	H		(165)
$4,6\text{-}(NO_2)_2\text{-}2\text{-}(HOOC)C_6H_2CO—$	H		(165)
$3\text{-}(NH_2)C_6H_4CO—$	H		(90)
$3,5\text{-}(NH_2)_2C_6H_3CO—$	H		(90)
$1\text{-}(NH_2SO_2)C_6H_4\text{-}4\text{-}NHCOCH_2CO—$	H		(123)
$1\text{-}(NHSO_2)C_6H_4\text{-}4\text{-}NHCOC(C_2H_5)_2CO—$	H		(123)

In substantiation of the statement that this is really an N^1-substituted derivative, note that all the N^4-sulfonylsulfanilamides are inactive except where the group is N^4-sulfanilyl or N^4-metanilyl, and the latter has practically no activity, as have most derivatives of *metanilamide.* On the other hand, substituted N^1-phenylsulfanilamides frequently show activity.

Note also that N^3-sulfanilylmetanilamide (correctly classed as an N^1-substituted sulfanilamide; see II (C) (4)) has more activity than N^4-metanilylsulfanilamide. This was predicted before synthesis, since the first com-

TABLE 33

N^4-Heterocyclic-acylsulfanilamides



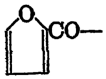
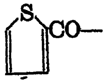
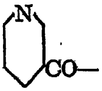
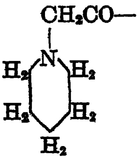
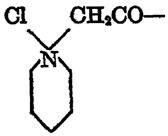
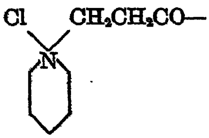
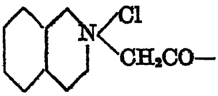
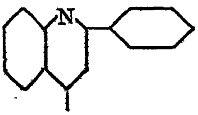
R⁴	R⁴′	ACTIVITY	REFERENCES
	H	±	(102)
	H	±	(102)
	H	+++	(43, 102, 157)
	H		(90)
	H		(90)
	H		(90)
	H		(90)
	H		(8)

TABLE 33—*Concluded*

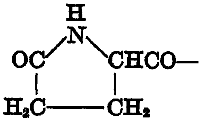
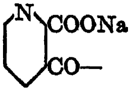
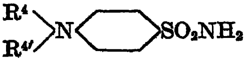
R^4	$R^{4'}$	ACTIVITY	REFERENCES
	H	+++	(70)
	H	++	(78, 165)

TABLE 34

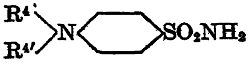
N^4-Acyclicsulfonylsulfanilamides



R^4	$R^{4'}$	ACTIVITY	REFERENCES
CH_3SO_2—	H	0, −	(174, 179)
$C_2H_5SO_2$—	H	0	(174)
$CH_3(CH_2)_3SO_2$—	H	0, −	(174, 179)
$CH_3(CH_2)_4SO_2$—	H	0	(174)
$CH_3(CH_2)_5SO_2$—	H	0	(174)
$CH_3(CH_2)_{11}SO_2$—	H	0	(174)

TABLE 35

N^4-Isocyclic-sulfonylsulfanilamides



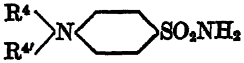
R^4	$R^{4'}$	ACTIVITY	REFERENCES
$C_6H_5SO_2$—	H	0	(174)
3-$(NO_2)C_6H_4SO_2$—	H		(90)
4-$(NO_2)C_6H_4SO_2$—	H		(90)
$C_6H_5OCH_2CH_2SO_2$—	H		(90)
2-CH_3O-5-$(CH_3)C_6H_3OCH_2CH_2CH_2SO_2$—	H		(90)
3,4-$(CH_3O)_2C_6H_3SO_2$—	H		(90)
3-$(HOOC)C_6H_4SO_2$—	H		(165)
3-$(NH_2)C_6H_4SO_2$—	H	±	(37, 90)
4-$(NH_2)C_6H_4SO_2$—	H*	+++, +	(6, 9, 11, 54, 70, 90, 121, 164)
4-[4′-$(NH_2)C_6H_4SO_2NH]C_6H_4SO_2$—	H	++	(9, 11, 37, 90)
4-[4′-$(CH_3CONH)C_6H_4SO_2NH]C_6H_4SO_2$—	H		(9, 37, 90)
4-[$(CH_3)_2N]C_6H_4SO_2$—	H		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	±	(90, 131)
$C_6H_5CH_2SO_2$—	H	0	(174)
4-$(NH_2SO_2)C_6H_4NHSO_2$—	H		(186)

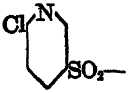
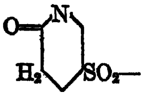
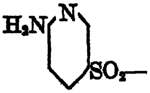
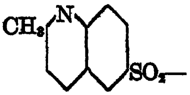
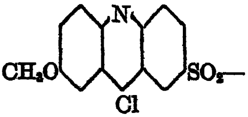
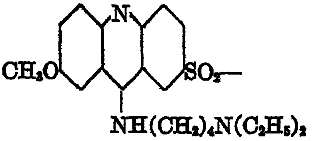
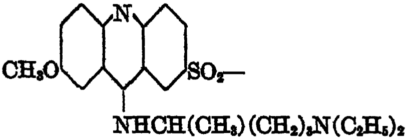
* Diseptyl C, Disulon.

pound is behaving as an N^1-substituted sulfanilamide and the second as an N^1-substituted metanilamide.

TABLE 36

N^4-Heterocyclic-sulfonylsulfanilamides



R^4	$R^{4'}$	ACTIVITY	REFERENCES
	H		(149)
	H		(150)
	H		(149)
	H		(90)
	H		(44)
	H		(44)
	H		(44)

Recent opinions on the effectiveness of N^4-sulfanilylsulfanilamide (54, 121) are that it is much less effective than was first believed against streptococci. It was inactive against pneumococci, but showed some activity against staphylococci.

The drug is used for treatment of gonorrhea, particularly in Europe, but has not gone beyond the clinical stage in this country, probably because of a few cases of peripheral neuritis reported as accompanying its use. The compound is considerably less soluble than sulfanilamide and is not as well absorbed.

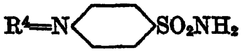
(G) *Anils (Schiff bases)*

The anils or Schiff bases derived from sulfanilamide have all been active (see tables 37 and 38). This is almost certain to be the result of breakdown to sulfanilamide on absorption, since the compounds are not especially stable chemically and their more stable reduction products are known to undergo cleavage (144). Small differences in activity may be explained by the results of different observers and of differences in absorption.

TABLE 37

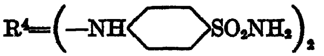
Acyclic anils of sulfanilamide

(a) N^4-Alkylidenesulfanilamides:



R^4	ACTIVITY	REFERENCES
$CH_2=$	+	(173, 193)
Sugar derivatives*:		
Xylose		(141)
Glucose	+	(19, 52, 104, 184)
Galactose		(141)
Tetraacetylgalactose		(141)
Lactose		(141)
Mannose		(104)
Arabinose		(104)
Maltose	++	(191)
$HOOCCH=$		(26)
$CH_3(HOOC)C=$		(26)

(b) N^4-Alkylidene-*bis*-sulfanilamides:



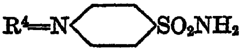
R^4	ACTIVITY	REFERENCES
$CH_3(CH_2)_6CH=$		(50)
$CH_3(CH_2)_7CH=$		(50)
$CH_3(CH_2)_9CH=$		(50)

* Sugar derivatives are classified here, although they are probably not anils but glucosides (see 104, 141).

Apparent exceptions are cases where the linkage is directly to a heterocyclic ring (see table 39). However, these derivatives are not true anils,

TABLE 38

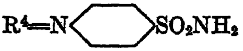
Isocyclic anils of sulfanilamide: N^4-aralkylidenesulfanilamides

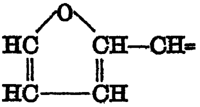
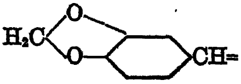
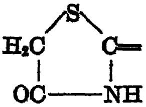
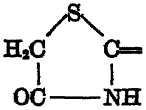


R^4	ACTIVITY	REFERENCES
$C_6H_5CH=$	++	(67, 102, 172)
$3\text{-}(NO_2)C_6H_4CH=$	+	(70)
$4\text{-}(NO_2)C_6H_4CH=$	++	(26)
$6\text{-}NO_2\text{-}3\text{-}(HO)C_6H_3CH=$	+	(70)
$C_6H_5CH{=}CHCH=$	+, +++	(70, 102)
$C_6H_5CH{=}CHCH=$ $(\cdot HCl)$		(169)
$C_6H_5CH{=}C(C_5H_{11})CH=$		(123)
$2\text{-}(HO)C_6H_4CH=$	++	(67, 155, 172)
$4\text{-}(HO)C_6H_4CH=$	+++	(67, 172, 178)
$4\text{-}(CH_3O)C_6H_4CH=$	++, +	(70, 101, 102)
$4\text{-}HO\text{-}3\text{-}(CH_3O)C_6H_3CH=$	+	(155)
$3,4\text{-}(CH_3O)_2C_6H_3CH=$	+	(70)
$3,4\text{-}(C_2H_5O)_2C_6H_3CH=$	+	(70)
$2\text{-}(HOOC)C_6H_4CH=$	++	(19)
$3\text{-}(HOOC)C_6H_4CH=$		(165)
$4\text{-}(CH_3)_2NC_6H_4CH=$	++	(70, 77, 101, 102)
$2,4\text{-}(HO)_2C_6H_3CH=$	++, +	(67, 155)
$2,4,6\text{-}(HO)_3C_6H_2CH=$	++	(67)

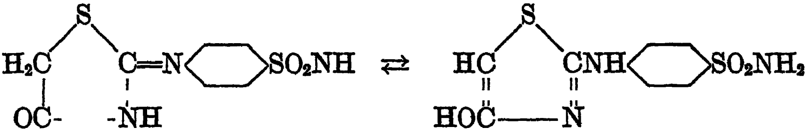
TABLE 39

Heterocyclic anils of sulfanilamide



R^4		
	+	(70)
	+	(70)
		(121)
		(121)

since they might equally well be written in tautomeric form, as in the pair:



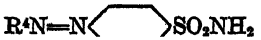
Since the reference gave the first formula, the compound has been indexed as an anil. Possibly it might better be classed as an N^4-heterocyclic-sulfanilamide.

(*H*) *Azo derivatives*

While by no means proved, it is nevertheless very likely that the therapeutic properties of the azo dyes derived from sulfanilamide are primarily the therapeutic properties of sulfanilamide itself, which has resulted from cleavage of the azo linkage *in vivo*. The early work of the Trëfouëls, Nitti, and Bovet (180) called attention to the fact that the azo compounds were not active *in vitro*, but showed activity *in vivo* for a wide variety of dyes as long as the sulfanilamide part of the molecule was not varied in structure, but when this was changed by replacing the sulfonamide group, the activity was lost. This indicated to them that sulfanilamide was the active form and led to discovery of its therapeutic properties. Later, Fuller (63) was able to isolate sulfanilamide from the urine of patients treated with Prontosil.

It seems probable that lack of absorption or resistance to cleavage will account for most inactive azo dyes derived from sulfanilamide.

The azo derivatives are taken up in the following order: (*1*) acyclic;



R^4	ACTIVITY	REFERENCE
$CH_3CO(HOOC)CH$—		(148)

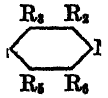
(*2*) isocyclic, including azo derivatives of benzene (table 40), azo derivatives of naphthalene (table 41), and miscellaneous derivatives (table 42); (*3*) heterocyclic, including azo derivatives of pyridine (table 43), azo derivatives of quinoline (table 44), and miscellaneous derivatives (table 45).

IV. NUCLEAR, N^1-SUBSTITUTED SULFANILAMIDES

No pharmacological data are available on these compounds. The compounds that have been synthesized are listed in table 46.

'ABLE 40

ivatives oj sulfanilam and

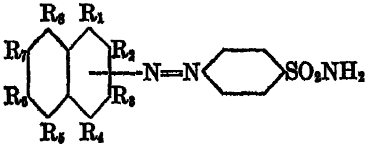


R_2	R_3	R_4	R_5	R_6	ACTIVITY	REFERENCES
						(30, 70, 91, 175)
		HO—			+	(67, 181)
CH_3—		HO—			+	(181)
	CH_3—	HO—			+	(181)
CH_3—		HO—	CH_3—		±	(181)
	CH_3—	HO—	CH_3—		±	(181)
CH_3—(?)	CH_3—(?)	HO—	Cl—(?)			(20, 86)
HO—	CH_3—		CH_3—		±	(181)
CH_3—		HO—	$(CH_3)_2CH$—			(20, 86)
CH_3—		HO—	$CH_3(CH_2)_2$—		±	(181)
HO—		HO—			+++	(67, 102, 181)
CH_3O—		HO—			+	(181)
	CH_3O—	HO—			+	(181)
HO—	$C_5H_{11}S$—		CH_3—		+	(102)
HO—		HO—	C_2H_5—		+	(181)
HO—		HO—	$CH_3(CH_2)_2$—		+	(181)
HO—		HO—	$CH_3(CH_2)_5$—		+	(181)
HO—		HO—		HO—	±	(67, 181)
HO—		HO—		C_2H_5O—	+	(181)
	HOOC—	HO—			+	(67, 102, 108)
	HOOC—	HS—				(67)
		NH_2SO_2—				(167, 175)

HO—			NH_2SO_2—		±	(138)
NH_2—			Cl—			(93)
Cl—		NH_2—				(93)
	Cl—	NH_2—				(93)
		$(CH_3)_2N$—				(68)
NH_2—		NH_2—	(Prontosil)		++	(86)
NH_2—		$(C_2H_5)_2N$—				(86)
$(C_2H_5)_2N$—		$(C_2H_5)_2N$—				(86)
NH_2—		HO—				(87)
HO—		NH_2—				(87)
$HOOCCH_2NH$—		NH_2—				(88)
NaO_3SNH—		HO—				(88)
Cl—		NaO_2SCH_2NH—				(93)
NaO_2SCH_2NH—		NaO_2SCH_2NH—				(88)
NH_2—		NH_2—	HO—			(86)
	HOOC—	NH_2—				(93)
NH_2—		NH_2—	HOOC—			(88)
NH_2—		NH_2—	(Rubiazol)	HOOC—	++	(106)
CH_3CONH—		NH_2—	HOOC—			(88)
NH_2—		NH_2—	HO_3S—			(88)
NH_2—		HO—	HO_3S—			(88)
CH_3CONH—		HO—	HO_3S—			(88)
HO—			$HOOC(NH_2)CH$—		++	(152)
	$(C_2H_5)_2N(CH_2)_3NH$—	HO—			±	(181)
CH_3—		$(NH_2CH_2CHOHCH_2)(C_2H_5)N$—			+	(48)

TABLE 41

derivatives of sulfanilamide and naphthalene

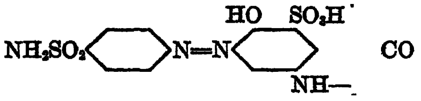


R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	ACTIVITY	REFERENCE
x	HO—								(66, 68)
x	HO—				NO_2—		HO_3S—		(88)
x			NH_2—	NH_2—					(86)
x			HO—	NH_2—					(87)
x	HO—	HOOC—			NH_2—				(88)
x	HO—				NH_2—		HO_3S—		(88)
x	NH_2—			HO—		HO_3S—			(88)
x	CH_3CONH—			HO—		HO_3S—			(88)
x	NH_2CONH—			HO—		HO_3S—			(88)
x	3-$(NH_2)C_6H_4CONH$—			HO—		HO_3S—			(88)
x	$NH_2C(NH)NHC(NH)(NH)$—			HO—		HO_3S—			(88)
x	NH_2OCCH_2NH—			HO—		HO_3S—			(88)
x	CH_3NH—			HO—		HO_3S—			(88)
x	$(C_2H_5)_2N$—			HO—		HO_3S—			(88)
	NH_2—				HO_3S—	x	HO—		(88)
	CH_3CONH—				HO_3S—	x	HO—		(88)
	CH_3CONH—	HO_3S—			HO_3S—	x	HO—*	++	(88)
C_6H_5CONH—			HO_3S—		HO_3S—	x	HO—		(88)

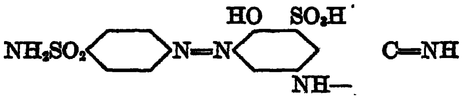
TABLE 42

Azo derivatives of sulfanilamide and miscellaneous isocyclic compounds

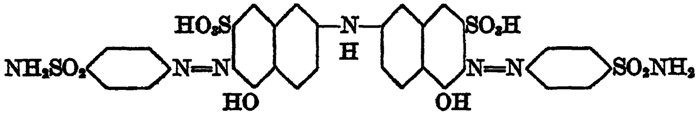
REFERENCES



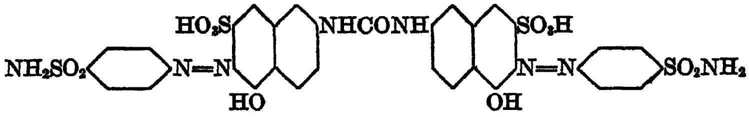
(88)



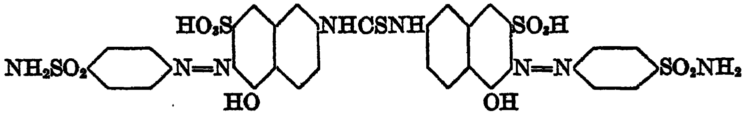
(88)



(88)



(88)



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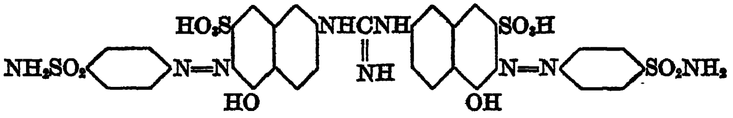
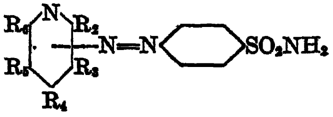


(88)

TABLE 43

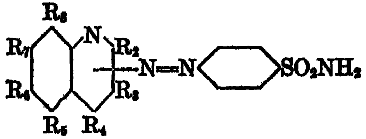
Azo derivatives of sulfanilamide and pyridine



R_2	R_3	R_4	R_5	R_6	ACTIVITY	REFERENCES
HO—			x	CH_3—		(87)
HO—		HO—	x	CH_3—		
NH_2—			x			(87)
NH_2—			x	—$NH_2 \cdot HCl$	+, 0	(33, 59, 60, 87)
HO—			x	—$NH_2 \cdot HCl$		(87)
NH_2—	HO_3S—		x	—NH_2		(88)

TABLE 44

Azo derivatives of sulfanilamide and quinoline

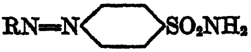


R_2	R_3	R_4	R_5	R_6	R_7	R_8	ACTIVITY	REFERENCES
								(87)
						CH_3—		(87)
			x	HO—				(87)
					HO—			(87)
						HO—		(87, 138)
				Cl—		HO—		(87)
			CH_3—			HO—		(87)
			x	HO—		HO—		(87)
			x		HOOC—	HO—		(88)
			HO_3S—		x	HO—		(88)
			—$NH_2 \cdot HCl$					(87)
			x	—$NH_2 \cdot HCl$				(87)
			x	C_2H_5NH—$\cdot HCl$				(87)
			x	$(CH_3)_2CH(CH_2)_5NH$—				(87)
			x	$CH_3(CH_2)_{11}NH$—				(87)
			x	$HOOCCH_2NH$—				(88)
			x	NH— | CH_2SO_2Na				(88)
			x	NH— | CH_2SO_3Na				(88)

					$-\underset{\substack{\vert \\ C_2H_5}}{N}H\cdot HCl$			(87)
					$-\underset{\substack{\vert \\ C_4H_9}}{N}H\cdot HCl$			(87)
			x			$-NH_2\cdot HCl$		(87)
			x	CH_3-		$-NH_2\cdot HCl$		(87)
			x	$HO-$		$-NH_2\cdot HCl$		(87)
			x	CH_3O-		$-NH_2$	0	(178)
			x	CH_3O-		$-NH_2\cdot HCl$		(87)
$HOOC-$		$HO-$		NH_2-				(88)

TABLE 45

Azo derivatives of sulfanilamide and miscellaneous heterocyclic compounds



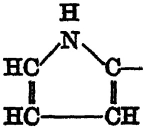
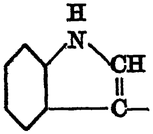
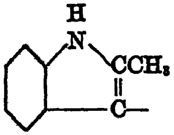
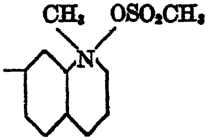
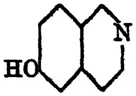
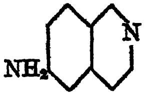
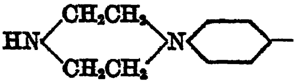
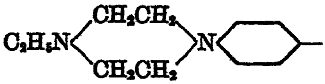
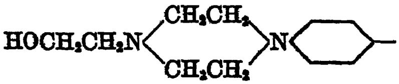
R	ACTIVITY	REFERENCES
	++	(161)
	++	(161)
	0	(161)
	0	(138)
		(87)
		(87)
		(99)
		(99)
		(99)

TABLE 45—*Continued*

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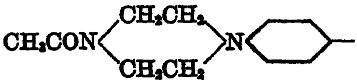
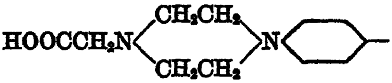
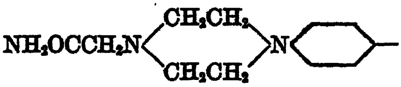
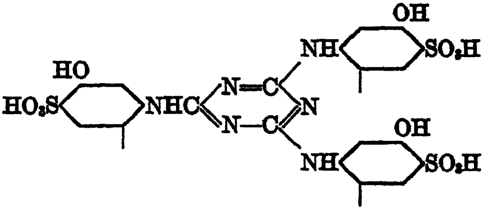
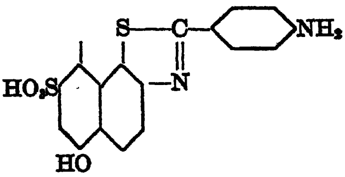
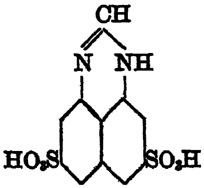
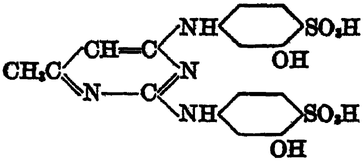
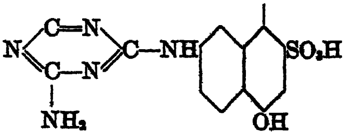
		(99)
		(99)
		(99)
		(88)
		(88)
		(88)
		(88)
		(88)

TABLE 45—*Concluded*

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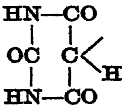
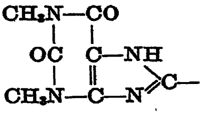
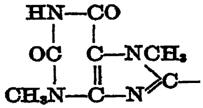
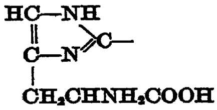
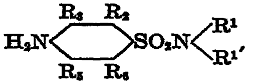
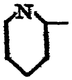
		(148)
	++	(137)
	++	(137)
	++	(152)
Dihydrocupreine	±	(20, 74)
Dihydrocupreidine	±	(20)
Apoquinine	±	(20)
Isoapoquinine	±	(20)
Casein	+	(178)
Antipneumococcus serum		(152)

TABLE 46

Nuclear, N^1-substituted sulfanilamides



R^1	$R^{1'}$	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCE
A. N^1-Inorganic substituents							
No examples							
B. N^1-Acyclic substituents							
CH_3—	H	C_2H_5—	H	H	H		(80)
$HOCH_2CH_2$—	H	H	CH_3O—	H	H		(85)
C. N^1-Isocyclic substituents							
C_6H_5—	H	NH_2—	H	NH_2SO_2—	H		(125)
C_6H_5—	H	NH_2—	H	$C_6H_5NHSO_2$—	H		(125)
C_6H_5—	H	H	$C_6H_5NHSO_2$—	$C_6H_5NHSO_2$—	H		(55)
$(CH_3)_2C_6H_3$—	H	H	Cl—	H	H		(12)
D. N^1-Heterocyclic substituents							
	H	H	NO_2—	H	H		(98)

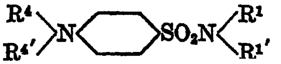
V. NUCLEAR,N^4-SUBSTITUTED SULFANILAMIDES

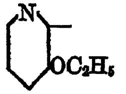
Of the few compounds in this group that have been studied, all have been found inactive (see table 47).

VI. N^1,N^4-SUBSTITUTED SULFANILAMIDES

In these derivatives, the compounds having a potentially free N^4-amino group have activities comparable with the corresponding N^1-substituted sulfanilamide. Where the amino group is blocked by a substituent such as alkyl, aryl, or sulfonyl, the compounds are inactive.

(*A*) *N^4-Inorganic-N^1-substituted sulfanilamides*



R⁴	R⁴′	R¹	R¹′	ACTIVITY	REFERENCE
HO—	H		H		(160)

(*B*, *C*, *D*) *N^4-Acyclic-, N^4-isocyclic-, and N^4-heterocyclic-N^1-substituted sulfanilamides*

No data on activity are available for most of the derivatives made (see tables 48, 49, and 50). The formaldehyde-sulfoxalate and formaldehyde-bisulfite derivatives of sulfapyridine and sulfathiazole have the activities of the parent compounds against both streptococci and pneumococci. Undoubtedly, they break down to the parent substances *in vivo.*

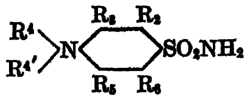
(*E*) *N^4-Acyl-N^1-substituted sulfanilamides*

This very large group of compounds covers practically all the N^1-substituted sulfanilamide derivatives of Class II, because of the fact that the N^4-acetyl derivatives are intermediates in synthesis. Comparatively few N^4-acetyl-N^1-substituted sulfanilamides have been studied, since the early work showed them to be much less active than the deacetylated products.

A number of longer chain N^4-acyl-N^1-substituted sulfanilamides have been made, but these are thought to be intrinsically no more active than the deacylated products. Substantial evidence for this belief is lacking. The proof would involve first the demonstration of free amine *in vivo,* and second, a comparison of S.B.C.$_{50}$'s measured against controls in which the blood level distribution was duplicated by administration of the free amine. The results of such experiments will be awaited with interest.

TABLE 47

Nuclear,N⁴-substituted sulfanilamides



R⁴	R⁴'	R₂	R₃	R₅	R₆	ACTIVITY	REFERENCES
A. *N*⁴-Inorganic substituents							
None							
B. *N*⁴-Acyclic substituents							
NaO_3SCH_2—	H	H	Cl—	H	H		(173)
NaO_3SCH_2—	H	H	CH_3O—	H	H		(173)
C. *N*⁴-Isocyclic substituents							
C_6H_5—	H	H	NO_2—	H	H		(55)
C_6H_5—	H	H	NH_2SO_2—	H	H		(55)
4-$(CH_3O)C_6H_4$—	H	H	HOOC—	H	H		(7)
D. *N*⁴-Heterocyclic substituents							
None							
E. *N*⁴-Acyl substituents (1) *N*⁴-Acetylsulfanilamides with inorganic nuclear substituents							
CH_3CO—	H	Cl—	H	H	H		(181)
CH_3CO—	H	H	Cl—	H	H		(173)

CH_3CO—	H	H	Br—	Br—	H		(167)
CH_3CO—	H	H	I—	H	H		(167)
CH_3CO—	H	H	I—	I—	H		(167)
CH_3CO—	H	H	NO_2—	H	H		(55, 97, 181)
CH_3CO—	H	HO—	H	H	H	0	(181)
CH_3CO—	H	H	CH_3O—	H	H		(173)
CH_3CO—	H	H	NH_2SO_2—	H	H		(55)
CH_3CO—	H	H	NH_2SO_2—	NH_2SO_2—	H		(125)
CH_3CO—	H	H	NH_2—	H	H	0	(86, 181)
CH_3CO—	H	NH_2—	H	NH_2SO_2—	H		(125)

E. N^4-Acyl substituents

(2) N^4-Acetylsulfanilamides with acyclic nuclear substituents

CH_3CO—	H	CH_3—	H	H	H	0	(84, 181)
CH_3CO—	H	H	CH_3—	H	H	0	(61, 84, 181)
CH_3CO—	H	CH_3—	H	Cl—	H		(84)
CH_3CO—	H	CH_3—	H	CH_3—	H		(84)
CH_3CO—	H	CH_3—	H	CH_3O—	H		(84)
CH_3CO—	H	H	CH_3O—	H	H		(173)
CH_3CO—	H	HOOC—	H	H	H	0	(96)
CH_3CO—	H	H	HOOC—	H	H	0	(96)

E. N^4-Acyl substituents

(3) N^4-Acyl substituents derived from carbonic acid

NH_2CO—	H	CH_3—	H	H	H	0	(34)
NH_2CO—	H	H	CH_3—	H	H	0	(34)
$CH_3CONHCO$—	H	CH_3—	H	H	H	0	(34)
$CH_3CONHCO$—	H	H	CH_3—	H	H	0	(34)

TABLE 47—*Concluded*

E. N^4-Acyl substituents

(4) N^4-Acyclic-acylsulfanilamides

R^4	$R^{4'}$	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
$ClCH_2CO—$	H	$CH_3—$	H	$C_2H_5O—$	H		(90)
$(CH_3)_2CHCH_2CO—$	H	$CH_3—$	H	Cl—	H		(84)
$(CH_3)_2CHCH_2CO—$	H	$CH_3—$	H	$CH_3O—$	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO—$	H	$CH_3—$	H	H	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO—$	H	H	$CH_3—$	H	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO—$	H	$CH_3—$	H	$CH_3—$	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO—$	H	$CH_3—$	H	$CH_3O—$	H		(25, 84)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO—$	H	$CH_3O—$	H	$CH_3O—$	H		(25, 84)
$C_4H_9NHCH_2CO—$	H	$CH_3—$	H	$C_2H_5O—$	H		(90)

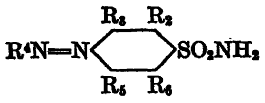
F. N^4-Sulfonyl substituents

R^4	$R^{4'}$	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
$C_6H_5O(CH_2)_3SO_2—$	H	$CH_3—$	H	$CH_3O—$	H		(90)
$4\text{-}(NH_2)C_6H_4SO_2—$	H	$CH_3—$	H	$CH_3O—$	H		(90)
$4\text{-}(CH_3CONH)C_6H_4SO_2—$	H	$CH_3—$	H	$CH_3O—$	H		(90)

G. N^4-Anils

None

H. N^4-Azosulfanilamides: isocyclic and heterocyclic



R^4	$R^{4'}$	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
$4\text{-}NH_2SO_2\text{-}2\text{-}IC_6H_3—$		H	I—	H	H		(167)

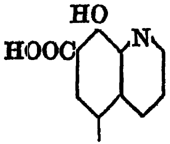
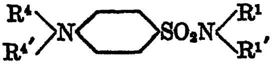
2,4-$(NH_2)_2C_6H_3$—	H	NH_2SO_2	H	H
2,4-$(NH_2)_2C_6H_3$—	CH_3	H	H	H
	H	CH_2—	H	H

TABLE 48

N⁴-Acyclic-N¹-substituted sulfanilamides



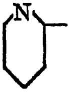
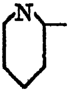
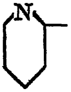
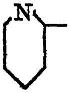
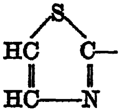
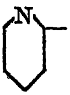
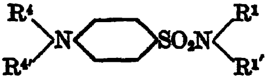
R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
CH_3—	H	$CH_3CHOHCH_2$—	H		(2)
CH_3—	CH_3—	C_6H_5—	H		(56)
CH_3—	H	CH_3—	CH_3—		(89)
CH_3—	CH_3—	4-(HOOC)C_6H_4—	H		(91)
CH_3—	H	4-(NH_2)C_6H_4—	H		(76)
CH_3—	H		H		(132)
CH_3—	CH_3—		H		(132)
CH_3—	CH_3—		CH_3—		(132)
CH_3CH_2—	H	$(CH_3)_2COHCH_2$—	H	0	(2)
NaO_2SCH_2—	H	$CH_3(CH_2)_{10}CO$—	H		(38)
NaO_2SCH_2—	H	NaO_2SCH_2—	H	—	(25, 95)
NaO_2SCH_2—	H		H	++	(96)
NaO_2SCH_2—	H		H	++	(123, 161)
NaO_3SCH_2—	H		H	++	(96)
NaO_3SCH_2—	H	4-(NH_2SO_2)C_6H_4—	H	±	(184)
$NaO_3SCH_2CHOHCH_2$—	CH_3—	CH_3—	CH_3—		(89)

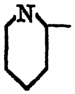
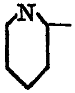
Table 51 includes all of the *N*⁴-acetyl-*N*¹-substituted sulfanilamides, with the latter substituents taken up in the following order: (a) inorganic substituents; (b) acyclic substituents; (c) isocyclic substituents (*1*)

C_nH_{2n-1} to C_nH_{2n-13}, (*2*) oxy or oxo, (*3*) carboxy, (*4*) sulfo, (*5*) amino; (d) heterocyclic substituents; (e) acyl substituents grouped as (*1*) carbonic acid acyl, (*2*) acyclic-acyl, (*3*) isocyclic-acyl, (*4*) heterocyclic-acyl; and (f) sulfonyl substituents. Table 52 contains all of the N^4-acyl-N^1-substituted sulfanilamides in which the group in the N^4-position is an acyl group other than acetyl. These acyl groups are taken up in the following order: (a) acyl groups derived from carbonic acid; (b) acyclic-acyl groups derived from (*1*) monobasic acids and (*2*) dibasic acids; (c) isocyclic-acyl groups; (d) heterocyclic-acyl groups.

TABLE 49

N^4-Isocyclic-N^1-substituted sulfanilamides



R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
$C_6H_5CH_2$—	H	$HOCH_2CH_2$—	H	±	(2)
$C_6H_5CH_2$—	H		H		(132)
2,4-$(NO_2)_2C_6H_3$—	H		H		(132)
4-$(CH_3O)C_6H_4CH_2$—	H	C_6H_5—	H	0	(102)

(*F*) *N^4-Sulfonyl-N^1-substituted sulfanilamides (see table 53)*

Few derivatives have been studied where the N^4-sulfonyl group is other than N^4-sulfanilyl and in the latter case the compounds are probably behaving as N^1-substituted sulfanilamides (see section III F). Uleron, which has had widespread use (particularly in Germany) for treatment of gonorrhea, has the disadvantage for this use of causing a high incidence of peripheral neuritis when treatment is sufficiently prolonged to be reasonably certain of cure. Its reported effectiveness against staphylococcus infections (48) has not been confirmed by others (140).

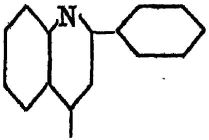
(*G*) *N^4-Anil-N^1-substituted sulfanilamides (see table 54)*

The N^4-anils derived from N^1-substituted sulfanilamides retain the activities of the parent compounds in most cases. The high activities claimed for the N^4-*p*-nitrobenzylidine derivatives are noteworthy.

TABLE 50

N⁴-Heterocyclic-N¹-substituted sulfanilamides

(1) *N*⁴-Nitrogen not in the heterocyclic system

R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
	H	C_6H_5—	C_2H_5—		(8)

(2) *N*⁴-Nitrogen in the heterocyclic system

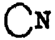
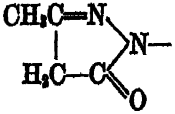
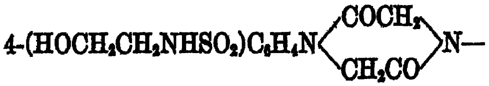
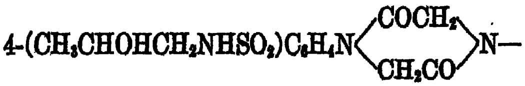
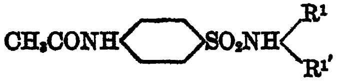
	R^1	$R^{1'}$	ACTIVITY	REFERENCES
	4-(HOOC)C_6H_4—	H		(79)
 $4\text{-}(HOCH_2CH_2NHSO_2)C_6H_4N\left\langle\begin{matrix}COCH_2\\CH_2CO\end{matrix}\right\rangle N\text{—}$	$HOCH_2CH_2$—	H	0	(1)
 $4\text{-}(CH_3CHOHCH_2NHSO_2)C_6H_4N\left\langle\begin{matrix}COCH_2\\CH_2CO\end{matrix}\right\rangle N\text{—}$	$CH_3CHOHCH_2$—	H	0	(1)

TABLE 51

N⁴-Acetyl-N¹-substituted sulfanilamides



R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
a. *N⁴*-Acetyl-*N¹*-inorganic sulfanilamides			
HO—	H		(114)
H_2N—	H	—	(179)
b. *N⁴*-Acetyl-*N¹*-acyclicsulfanilamides			
CH_3—	H	+	(20, 61, 181)
C_2H_5—	H	+	(20, 61, 181)
$CH_3(CH_2)_2$—	H	±	(61, 181)
$(CH_3)_2CHCH_2$—	H	±	(61, 181)
CH_2═CH—CH_2—	H	±	(181)
CH_3—	CH_3—	+	(61, 164, 181)
C_2H_5—	C_2H_5—	+	(61, 70, 181)
$CH_3(CH_2)_2$—	$CH_3(CH_2)_2$—	±	(61, 181)
$HOCH_2CH_2$—	H—	0, ±	(2, 42, 114, 121)
$HOCH_2CH_2$—	CH_3—	0	(42, 121)
$HOCH_2CH_2$—	$HOCH_2CH_2$—	0	(2, 42, 87, 100, 102)
$HOCH_2CH_2CH_2$—	H	0	(2, 85, 114)
$CH_3CHOHCH_2$—	H	±	(2, 42, 114)
$HOCH_2CH(OH)CH_2$—	H	0	(2, 114)
$CH_3CH(OH)CH_2$—	$CH_3CHOHCH_2$—		(42)
$(CH_3)_2COHCH_2$—	H	±	(2)
$C_2H_5CH(OH)CH_2$—	H		(114)
$(HOCH_2)(CH_3)_2C$—	H		(42)
$(HOCH_2)_2CH$—	H		(114)
$(HOCH_2)_2(CH_3)C$—	H		(42)
$HOCH_2(CHOH)_4CH_2$—	CH_3—	0	(2)
$HOOCCH_2$—	H	+	(21, 82, 100, 102)
$NaOOCCH_2$—	H	0	(121)
$C_2H_5OOCCH_2$—	H		(65)
$HOOCCH_2CH_2(HOOC)CH$—	H		(21)
$HOOC(CH_3)CH$—	H		(136)
$NaOOC(CH_3)CH$—	H	0	(121)
$HO_3SCH_2CH_2$—	H		(82)
$(C_2H_5)_2NCH_2CH_2$—	H	0	(121)
$(C_2H_5)_2N(CH_2)_3$—	H	0	(181)
$(C_2H_5)_2N(CH_2)_4$—	H		(28, 29)

TABLE 51—*Continued*

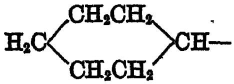
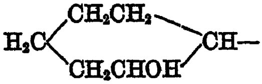
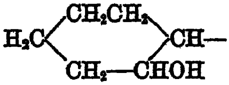
R^1	$R^{1'}$	ACTIVITY	REFERENCES
c-1. N^4-Acetyl-N^1-isocyclicsulfanilamides: $R = C_nH_{2n-1}$ to C_nH_{2n-13}			
	H		(70)
	H	0	(121)
C_6H_5—	H	±	(20, 66, 91, 181)
C_6H_5—	$HOCH_2CH_2$—		(42)
2-ClC_6H_4—	H		(42)
4-ClC_6H_4—	H		(42)
2-$(NO_2)C_6H_4$—	H		(100, 187)
3-$(NO_2)C_6H_4$—	H		(187)
4-$(NO_2)C_6H_4$—	H		(9, 76, 187)
2-$(CH_3)C_6H_4$—	H		(66)
3-$(CH_3)C_6H_4$—	H		(66)
4-$(CH_3)C_6H_4$—	H		(91, 66)
$C_6H_5CH_2$—	H	±	(78, 181)
1-$C_{10}H_7$—	H		(66)
2-$C_{10}H_7$—	H		(66)
c-2. N^4-Acetyl-N^1-isocyclicsulfanilamides: oxy or oxo derivatives			
	H	0	(2)
2-$(HO)C_6H_4$—	H	0	(42, 121, 187)
3-$(HO)C_6H_4$—	H	0	(121, 187)
4-$(HO)C_6H_4$—	H	0	(42, 121, 187)
4-HO-2-$(NO_2)C_6H_3$—	H	0	(121)
4-HO-3-$(NO_2)C_6H_3$—	H	0	(121)
2-$(CH_3O)C_6H_4$—	H	0	(42)
3-$(CH_3O)C_6H_4$—	H		
4-$(CH_3O)C_6H_4$—	H		(28, 29)
4-$(HOCH_2)C_6H_4$—	H		(91)
4-$(C_2H_5)C_6H_4$—	H	±	(166, 181)
4-$(HS)C_6H_4$—	H		(91)
5-HS-2-$(CH_3)C_6H_3$—	H		(91)
2-$(OHC)C_6H_4$—	H		(91)
4-$(CH_3CO)C_6H_4$—	H		(197)
4-$(CH_3CH_2CO)C_6H_4$—	H		(197)
4-$(C_6H_5CO)C_6H_4$—	H		(197)

TABLE 51—*Continued*

R^1	$R^{1'}$	ACTIVITY	REFERENCES
c-3. N^4-Acetyl-N^1-isocyclicsulfanilamides: carboxy derivatives			
2-(HOOC)C_6H_4—	H	0	(35, 37, 100, 102, 121)
3-(HOOC)C_6H_4—	H		(35, 91, 100 102)
4-(HOOC)C_6H_4—	H	0	(9, 35, 91, 100, 102, 121)
3-(HOOCCH=CH)C_6H_4—	H		(65)
4-(HOOCCH=CH)C_6H_4—	H		(65)
4-(C_2H_5OOC)C_6H_4—	H		(29, 91)
3-(CN)C_6H_4—	H		(91)
4-(NH_2OC)C_6H_4—	H		(91)
2-CN-4-ClC_6H_3—	H		(91)
4-NO_2-2-(HOOC)C_6H_3—	H		(91)
4-HOOC-3-(HO)C_6H_3—	H		(42, 91)
4-(HO)$C_6H_4CH_2$(HOOC)CH—	H		(136)
c-4. N^4-Acetyl-N^1-isocyclicsulfanilamides: sulfo derivatives			
2-(HO_3S)C_6H_4—	H		(23, 35)
3-(HO_3S)C_6H_4—	H		(35)
4-(HO_3S)C_6H_4—	H		(35, 65, 91, 100, 102)
4-(HO_3S)C_6H_4—	C_2H_5—		(42)
4-(ClO_2S)C_6H_4—	H		(91)
4-($C_6H_5O_3S$)C_6H_4—	H		(91)
2,6-$(NO_2)_2$-4-(HO_3S)C_6H_2—	H		(91)
4-ClO_2S-2-(CH_3)C_6H_3—	H		(91)
4-HO_3S-1-$C_{10}H_6$—	H		(35, 91)
4-NaO_3S-1-$C_{10}H_6$—	H	0	(121)
7-HO_3S-5-HO-2-$C_{10}H_5$—	H		(91)
6-HO_3S-8-HO-2-$C_{10}H_5$—	H		(91)
3,6-$(HO_3S)_2$-1-$C_{10}H_5$—	H		(91)
3,8-$(HO_3S)_2$-1-$C_{10}H_5$—	H		(91)
4,8-$(NaO_3S)_2$-1-$C_{10}H_5$—	H	0	(121)
3,6,8-$(NaO_3S)_3$-1-$C_{10}H_4$—	H	0	(121)
c-5. N^4-Acetyl-N^1-isocyclicsulfanilamides: amino derivatives			
2-(NH_2)C_6H_4—	H	0	(121)
3-(NH_2)C_6H_4—	H	0	(121)
4-(NH_2)C_6H_4—	H	+	(76, 102, 121)
4-(CH_3CONH)C_6H_4—	H		(76, 84, 131)
4-[$CH_3CO(CH_3)N$]C_6H_4—	H		(76)
4-(C_6H_5CH=N)C_6H_4—	H	+	(102)
4-[4'-(NO_2)C_6H_4CH=N]C_6H_4—	H		(102)

TABLE 51—*Continued*

c-5. N^4-Acetyl-N^1-isocyclicsulfanilamides: amino derivatives—*Continued*

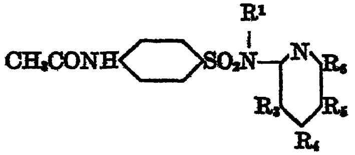
R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
$4\text{-}[4'\text{-}(CH_3O)C_6H_4CH{=}N]C_6H_4\text{—}$	H	+++	(102)
$4\text{-}[4'\text{-}[(CH_3)_2N]C_6H_4CH{=}N]C_6H_4\text{—}$	H	++	(102)
$2,4\text{-}(CH_3CONH)_2C_6H_3\text{—}$	H		(84)
$3,4\text{-}(CH_3CONH)_2C_6H_3\text{—}$	H		(131)
$4\text{-}[4'\text{-}(NH_2)C_6H_4NH]C_6H_4\text{—}$	H		(131)
$3\text{-}HO\text{-}4\text{-}(CH_3CONH)C_6H_3\text{—}$	H		(84, 131)
$2\text{-}CH_3\text{-}5\text{-}(CH_3CONH)C_6H_3\text{—}$	H		(76)
$5\text{-}CH_3\text{-}2\text{-}(CH_3CONH)C_6H_3\text{—}$	H		(76)
$3\text{-}CH_3\text{-}4\text{-}(CH_3CONH)C_6H_3\text{—}$	H		(84)
$2,3\text{-}(CH_3)_2\text{-}4\text{-}(CH_3CONH)C_6H_2\text{—}$	H		(76)
$4\text{-}[(CH_3)_2N]C_6H_4\text{—}$	H		(84)
$4\text{-}[(C_2H_5)_2N]C_6H_4\text{—}$	H		(76)
$4\text{-}(C_6H_5NH)C_6H_4\text{—}$	H		(84)
$2,6\text{-}(HO_3S)_2\text{-}4\text{-}(NH_2)C_6H_2\text{—}$	H		(91)

d-1. N^4-Acetyl-N^1-heterocyclicsulfanilamides: one oxygen or sulfur atom in the heterocyclic system

None

d-2. N^4-Acetyl-N^1-heterocyclicsulfanilamides: one nitrogen in the heterocyclic system

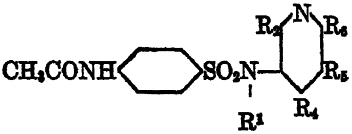
(a) 2-(N^4-Acetylsulfanilamido)pyridines



R^1	R_3	R_4	R_5	R_6	ACTIVITY	REFERENCES
						(39, 68, 129, 132, 159, 183, 189, 190)
Na—						(129)
$CH_3\text{—}$						(132)
$C_6H_5CH_2\text{—}$						(132)
			I—			(132)
			$NO_2\text{—}$			(132)
				$CH_3\text{—}$		(132, 183)
	HOOC—		$C_6H_5O_3S\text{—}$			(132)
			$NH_2\text{—}$	H		(160)
				$NH_2\text{—}$	+, ++	(33, 59, 60, 183)
				$4\text{-}(NH_2)\text{-}C_6H_4SO_2NH\text{—}$		(132)

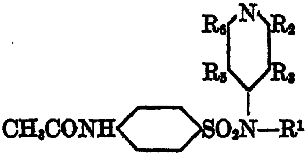
TABLE 51—*Continued*

d-2 (b). 3-(N^4-Acetylsulfanilamido)pyridines



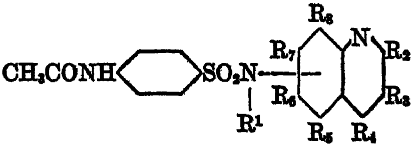
R^1	R_2	R_4	R_5	R_6	ACTIVITY	REFERENCES
						(132, 190)
				CH₃CONH—		(190)

d-2 (c). 4-(N^4-Acetylsulfanilamido)pyridines



R^1	R_3	R_5	R_2	R_6	ACTIVITY	REFERENCE
						(132)

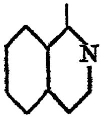
d-2 (d). x-(N^4-Acetylsulfanilamido)quinolines



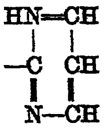
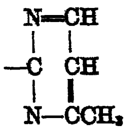
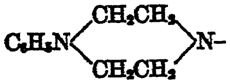
R^1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	ACTIVITY	REFERENCES
	x								(132, 183)
		x							(190)
				x					(14, 190)
					x				(14, 132, 190)
						y			(14)
							x		(14, 29, 190)
	CH_3—				x				(132)
	C_6H_5—		x						(8)
				x			CH_3O—		(132)
					CH_3O—		x		(29)
	HO—		CH_3—			x			(132)
	C_6H_5—		x		CH_3O—				(8)

TABLE 51—*Continued*

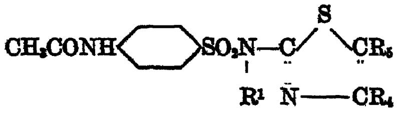
d-2 (e). Miscellaneous N^4-acetyl-N^1-heterocyclicsulfanilamides with one nitrogen atom in the heterocyclic system (general formula as at top of table)

R^1	$R^{1'}$	ACTIVITY	REFERENCE
	H		(132)

d-3. N^4-Acetyl-N^1-heterocyclicsulfanilamides with two or more nitrogen atoms in the heterocyclic system (general formula as at top of table)

R^1	$R^{1'}$	REFERENCES
		(159)
		(159)
		(99)

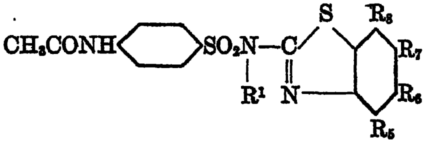
d-4 (a). N^4-Acetyl-N^1-heterocyclicsulfanilamides with one nitrogen atom and one oxygen (or sulfur) atom in the heterocyclic system: 2-(N^4-acetylsulfanilamido)thiazoles



R^1	R_4	R_5	ACTIVITY	REFERENCES
				(59, 124, 133, 159)
	CH_3—			(59, 124, 133, 159, 183)
$C_6H_5CH_2$—	CH_3—			(133)
		CH_3—		(133)
	C_6H_5—			(133)
	CH_3—	C_6H_5—		(133)
	CH_3—	$HOCH_2CH_2$—		(133)
	CH_3—	C_2H_5OOC—		(133)

TABLE 51—*Continued*

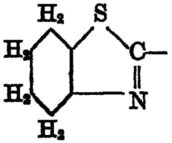
d-4 (b). 2-(N^4-Acetylsulfanilamido)benzothiazoles



R¹	R₅	R₆	R₇	R₈	ACTIVITY	REFERENCES
						(133)
C_2H_5—						(133)
			NO_2—			(133)
			C_2H_5O—			(133)
		CH_3CONH—				(133)

d-4 (c). Miscellaneous N^4-acetyl-N^1-heterocyclicsulfanilamides with one nitrogen, oxygen, or sulfur atom in the heterocyclic system

(general formula as at top of table)

R¹	R¹′	ACTIVITY	REFERENCE
	H		(60)

d-5. N^4-Acetyl-N^1-heterocyclicsulfanilamides with two nitrogen atoms and one oxygen (or sulfur) atom in the heterocyclic system

(general formula as at top of table)

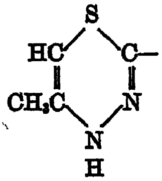
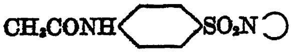
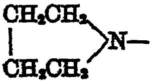
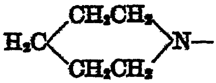
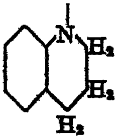
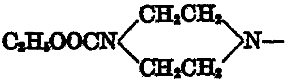
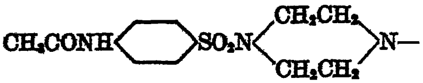
R¹	R¹′	ACTIVITY	REFERENCE
	H		(60)

TABLE 51—*Continued*

d-6. N^4-Acetyl-N^1-heterocyclicsulfanilamides with the N^1-nitrogen in the heterocyclic system



N◯	ACTIVITY	REFERENCES
		(88)
	0	(68, 70, 86, 87, 88)
	0	(178)
		(98)
		(42, 98)

e. N^4-Acetyl-N^1-acylsulfanilamides (general formula as at top of table)

e-1. N^4-Acetyl-N^1-inorganicsulfanilamides

R^1	$R^{1'}$		REFERENCES
CH_3NHCO—	H	0	(121)
$NH_2C(=NH)$—	H	0	(121)

e-2. N^4-Acetyl-N^1-acyclic-acylsulfanilamides

R^1	$R^{1'}$		REFERENCES
CH_3CO—	H		(38, 168)
CH_3CH_2CO—	H		(38)
$(CH_3)_2CHCO$—	H		(38)
$CH_3(CH_2)_2CO$—	H		(38)
$(CH_3)_2CHCH_2CO$—	H		(38)
$(C_2H_5)_2CHCO$—	H		(38)
$CH_3(CH_2)_4CO$—	H		(38)
$CH_3(CH_2)_5CO$—	H		(38)
$CH_3(CH_2)_6CO$—	H		(38)
$CH_3(CH_2)_3CH(C_2H_5)CO$—	H		(38)

TABLE 51—*Concluded*

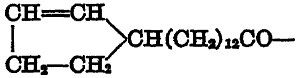
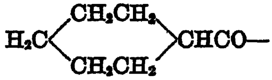
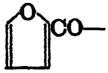
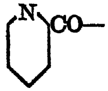
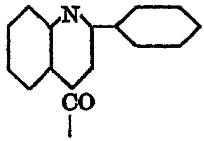
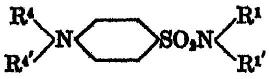
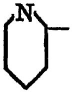
R^1	$R^{1'}$	ACTIVITY	REFERENCES
e-2. N^4-Acetyl-N^1-acyclic-acylsulfanilamides—*Continued*			
$CH_3(CH_2)_3CH(C_2H_5)CO—$	Na—		(38)
$CH_3(CH_2)_3CH(C_2H_5)CO—$	½Mg—		(38)
$CH_3(CH_2)_8CO—$	H		(38)
$CH_3(CH_2)_9CO—$	H		(38)
$CH_3(CH_2)_{10}CO—$	H		(38)
$CH_3(CH_2)_{12}CO—$	H		(38)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO—$	H		(38)
e-3. N^4-Acetyl-N^1-isocyclic-acylsulfanilamides			
	H		(38)
	H		(38)
$C_6H_5CO—$	H		(38)
$C_6H_5CH_2CH_2CO—$	H		(38)
$C_6H_5CH{=}CHCO—$	H		(38)
$(C_6H_5)_2CHCO—$	H		(38)
$4\text{-}(NO_2)C_6H_4CO—$	H		(38)
$4\text{-}(HOOC)C_6H_4CO—$	H		(42)
$4\text{-}(NH_2)C_6H_4CO—$	H		(38)
e-4. N^4-Acetyl-N^1-heterocyclic-acylsulfanilamides			
	H		(38)
	H		(38, 43)
	H		(38)
f. N^4-Acetyl-N^1-sulfonylsulfanilamides (general formula as at top of table)			
$n\text{-}C_5H_{11}SO_2—$	H		(174)
$4\text{-}(NH_2)C_6H_4SO_2—$	H		(151)
$CH_3CONHC_6H_4SO_2—$	H	±	(19, 36)
$CH_3CONHC_6H_4SO_2—$	$CH_3—$		(36)
$CH_3CONHC_6H_4SO_2—$	$C_2H_5—$		(36)

TABLE 52

*N*⁴-Acyl(other than acetyl)-*N*¹-substituted sulfanilamides



R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
a. *N*⁴-Substituents derived from carbonic acid					
$C_2H_5OCO—$	H	$HOCH_2CH_2—$	H	+	(2)
$C_2H_5OCO—$	H	$CH_3CHOHCH_2—$	H	±	(2)
$C_2H_5OCO—$	H	Morpholide		0	(2)
$NH_2CO—$	H	$C_2H_5—$	$C_2H_5—$	0	(34)
$CH_2{=}CHCH_2NHC({=}S)—$	H	$CH_3—$	$CH_3—$		(65)
$CH_2{=}CHCH_2NHC({=}S)—$	H	$4\text{-}(HO_3S)C_6H_4—$	H		(65)
$CH_2{=}CHCH_2NHC({=}S)—$	H	$4\text{-}(NH_2SO_2)C_6H_4—$	H		(65)
b. *N*⁴-Acyclic-acyl: (1) derivatives of monobasic acids					
$HCO—$	H		H		(123)
$CH_3CO—$	$CH_3—$	$4\text{-}(NO_2)C_6H_4—$	H		(76)
$CH_3CO—$	$CH_3—$	$4\text{-}CH_3COO\text{-}3\text{-}(NO_2)C_6H_3—$	H	0	(121)
$CH_3CO—$	$CH_3—$	$4\text{-}(CH_3CONH)C_6H_4—$	H		(76)
$CH_3CO—$	$C_2H_5—$	$(CH_3)_2C(OH)CH_2—$	H		(2)
$ClCH_2CO—$	H	$CH_3—$	H		(90)
$ClCH_2CO—$	H	$C_2H_5—$	$C_2H_5—$		(90)
$ClCH_2CO—$	H	$C_4H_9—$	H		(90)
$ClCH_2CO—$	H	$C_6H_5—$	H		(154)
$ClCH_2CO—$	H	$C_6H_5CH_2—$	H		(90)

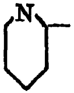
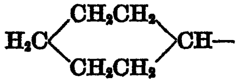
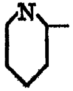
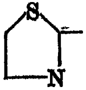
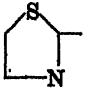
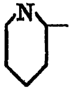
CH_3CH_2CO—	H	$CH_3CHOHCH_2$—	H	±	(2)
CH_3CH_2CO—	H	$(CH_3)_2C(OH)CH_2$—	H	±	(2)
CH_3CH_2CO—	H	4-$(CH_3CONH)C_6H_4$—	H		(76)
CH_3CH_2CO—	H	Morpholide		±	(2)
$CH_3(CH_2)_2CO$—	H	HO—	H	+	(146)
$CH_3(CH_2)_2CO$—	Cl—	Na—	Cl—		(42)
$CH_3(CH_2)_2CO$—	H	$HOCH_2CH_2$—	H	±	(2)
$CH_3(CH_2)_2CO$—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—	0	(2)
$CH_3(CH_2)_2CO$—	H	$CH_3CHOHCH_2$—	H	0	(2)
$CH_3(CH_2)_2CO$—	H	$(CH_3)_2C(OH)CH_2$—	H	±	(2)
$CH_3(CH_2)_2CO$—	H	Morpholide		±	(2)
$CH_3(CH_2)_2CO$—	H		H		(42)
$(CH_3)_2CHCO$—	H	HO—	H	±	(146)
$(CH_3)_2CHCO$—	H	$HOCH_2CH_2$—	H	+	(2)
$(CH_3)_2CHCO$—	H	$CH_3CHOHCH_2$—	H	±	(2)
$(CH_3)_2CHCO$—	H	$(CH_3)_2C(OH)CH_2$—	H	+	(2)
$(CH_3)_2CHCO$—	H	Morpholide		±, 0	(2, 121)
$CH_3(CH_2)_3CO$—	H	HO—	H	++	(146)
$CH_3(CH_2)_3CO$—	H	$CH_3CHOHCH_2$—	H	±	(2)
$CH_3(CH_2)_3CO$—	H	$(CH_3)_2C(OH)CH_2$—	H	±, 0	(2, 121)
$(CH_3)_2CHCH_2CO$—	H	HO—	H	±	(146)
$(CH_3)_2CHCH_2CO$—	H	$(CH_3)_2C(OH)CH_2$—	H	0	(2)
$(CH_3)_2CHCH_2CO$—	H		H		(84)
$CH_3(CH_2)_4CO$—	H	HO—	H	++	(146)
$CH_3(CH_2)_4CO$—	H	C_6H_5—	H	++	(102)
$CH_3(CH_2)_4CO$—	H	4-$(NO_2)C_6H_4$—	H	++	(102)

TABLE 52—*Continued*

R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCES
$CH_3(CH_2)_4CO—$	H	4-$(NH_2)C_6H_4—$	H	++	(102)
$CH_3(CH_2)_4CO—$	H		H	++	(102)
$CH_3(CH_2)_4CO—$	H		H	++	(174)
$CH_3(CH_2)_4CO—$	H	$CH_3(CH_2)_3SO_2—$	H	±	(174)
$CH_3(CH_2)_4CO—$	H	$CH_3(CH_2)_4SO_2—$	H	±	(174)
$CH_3(CH_2)_4CO—$	H	4-$(NH_2)C_6H_4SO_2—$	H		(42)
$(CH_3)_2CH(CH_2)_2CO—$	H	HO—	H	±	(146)
$(C_2H_5)_2CHCO—$	H		H		(123)
$CH_3(CH_2)_5CO—$	H	HO—	H	++	(146)
$CH_3(CH_2)_6CO—$	H	HO—	H	+	(146)
$CH_3(CH_2)_7CO—$	H	HO—	H	±	(146)
$CH_3(CH_2)_7CO—$	H		H		(42)
$CH_3(CH_2)_{10}CO—$	H	$C_4H_9—$	H		(84)
$CH_3(CH_2)_{10}CO—$	H	$C_6H_5CH_2—$	H		(84)
$CH_3(CH_2)_{10}CO—$	H	Piperidide			(84)
$CH_3(CH_2)_{10}CO—$	H	$CH_3(CH_2)_{10}CO—$	H	0	(38)

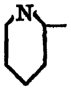
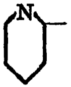
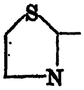
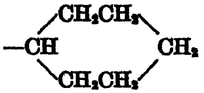
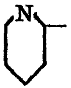
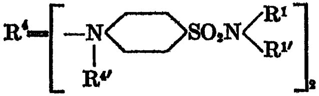
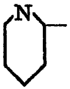
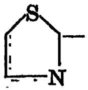
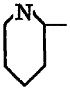
$CH_3(CH_2)_{10}CO$—	H		H	±	(42, 54)
$CH_3(CH_2)_{10}CO$—	H	4-$(NH_2)C_6H_4SO_2$—	H	0	(42)
$HOCH_2CO$—	H		H		(123)
$HOCH_2CO$—	H		H		(123)
CH_3OCH_2CO—	H	$HOCH_2CH_2$—	H	+, 0	(1, 121)
CH_3OCH_2CO—	H	CH_3OCH_2—	H	±	(121)
CH_3OCH_2CO—	H	$CH_3CHOHCH_2$—	H	0	(121)
CH_3COOCH_2CO—	H	$HOCH_2CH_2$—	H	0	(121)
CH_3COOCH_2CO—	H	$CH_3CHOHCH_2$—	H	0	(121)
CH_3COOCH_2CO—	H	$(CH_3)_2C(OH)CH_2$—	H	0	(121)
$C_2H_5OCH_2CO$—	H	CH_3—	CH_3—		(90)
$C_2H_5OCH_2CO$—	H	$C_6H_5CH_2$—	H		(90)
$C_2H_5OCH_2CO$—	H	Piperidide			(90)
$C_2H_5OCH_2CO$—	H		H		(90)
$HOOCCH_2CO$—	H	CH_3—	CH_3—		(89)
$HOOC(C_2H_5)_2CCO$—	H		H		(115)
$HOOC(CH_2)_2CO$—	H	$CH_3CHOHCH_2$—	H	0	(1)

TABLE 52—*Continued*

R^{4}	$R^{4'}$	R^{1}	$R^{1'}$	ACTIVITY	REFERENCES
$C_2H_5OOC(CH_2)_2CO—$	H	$CH_3CHOHCH_2—$	H	±	(1)
$CH_3(CH_3COO)CHCO—$	H	$CH_3CHOHCH_2—$	H	0	(1)
$HOCH_2CH_2NHCO(CH_2)_2CO—$	H	$HOCH_2CH_2—$	H	0	(1)
$C_4H_9NHCH_2CO—$	H	$C_4H_9—$	H		(90)
$C_4H_9NHCH_2CO—$	H	$HOCH_2CH_2—$	H		(90)
$C_4H_9NHCH_2CO—$	H	$C_6H_5CH_2—$	H		(90)
b. N^{4}-Acyclic-acyl: (2) derivatives of dibasic acids					
$—COCH_2CO—$	H	$HOCH_2CH_2—$	H	0	(1)
$—COCH_2CO—$	H	$CH_3CHOHCH_2—$	H	0	(1)
$—COCH_2CO—$	H		H		(123)
$—COCH_2CO—$	H		H		(123)
$—COCH_2CH_2CO—$	H	$HOCH_2CH_2—$	H	0	(1)
$—COCH_2CH_2CO—$	H	$CH_3CHOHCH_2—$	H	0	(1)
$—COCH_2CH_2CH_2CO—$	H	$HOCH_2CH_2—$	H	0	(1)
$—COCH_2CH_2CH_2CO—$	H	$CH_3CHOHCH_2—$	H	0	(1)
$(C_2H_5)_2C\begin{matrix}CO— \\ CO—\end{matrix}$	H		H		(123)

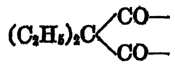
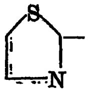
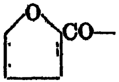
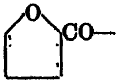
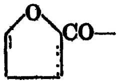
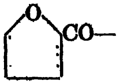
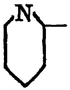
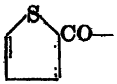
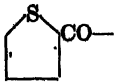
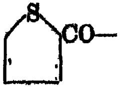
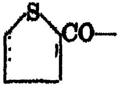
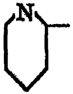
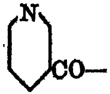
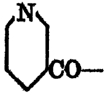
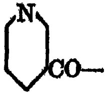
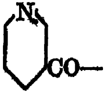
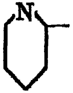
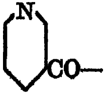
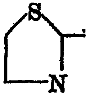
 $(C_2H_5)_2C\begin{matrix}CO—\\CO—\end{matrix}$	H		H		(123)
c. N^4-Isocyclic-acyl (general formula as at top of table)					
$C_6H_5CO—$	H	$C_6H_5—$	H	0	(143)
$C_6H_5CO—$	H	$3\text{-}(NO_2)C_6H_4—$	H		(76)
$C_6H_5CH{=}CHCO—$	H	$C_2H_5—$	$C_2H_5—$		(84)
d. N^4-Heterocyclic-acyl (general formula as at top of table)					
	H	$C_6H_5—$	H	±	(102)
	H	$4\text{-}(NO_2)C_6H_4—$	H	±	(102)
	H	$4\text{-}(NH_2)C_6H_4—$	H	±	(102)
	H		H	++	(102)
	H	$C_6H_5—$	H	±	(102)
	H	$4\text{-}(NO_2)C_6H_4—$	H	±	(102)

TABLE 52—*Concluded*

R⁴	R⁴′	R¹	R¹′	ACTIVITY	REFERENCES
	H	4-$(NH_2)C_6H_4$—	H	±	(102)
	H		H	±	(102)
	H	C_6H_5—	H		(102)
	H	4-$(NO_2)C_6H_4$—	H	0	(102)
	H	4-$(NH_2)C_6H_4$—	H		(102)
	H		H		(102, 119)
	H		H		(60)

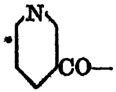
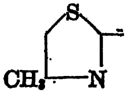
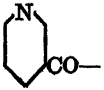
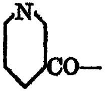
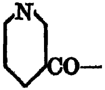
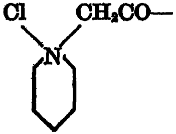
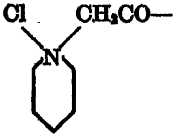
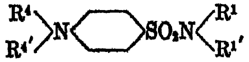
	H		H		(60)
	H	CH_3CO—	H		(43)
	H		H		(43)
	H	CH_3—	H		(90)
	H	C_2H_5—	C_2H_5—		(90)

TABLE 53

N^4-Sulfonyl-N^1-substituted sulfanilamides

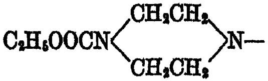
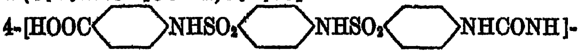


R^4	$R^{4'}$	R^1	$R^{1'}$	ACTIVITY	REFERENCE
1. N^4-Acyclic-sulfonyl					
CH_3SO_2—	H	CH_3—	CH_3—	−	(179)
CH_3SO_2—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—		(179)
CH_3SO_2—	H	4-$(NH_2SO_2)C_6H_4$—	H		(179)
2. N^4-Isocyclic-sulfonyl					
$C_6H_5SO_2$—	H	CH_3—	CH_3—		(26)
$C_6H_5SO_2$—	H	C_2H_5—	C_2H_5—		(26)
4-$BrC_6H_4SO_2$—	H	CH_3—	H		(90)
3-$(NO_2)C_6H_4SO_2$—	H	3-$(NO_2)C_6H_4SO_2$—	H		(36)
4-$(NO_2)C_6H_4SO_2$—	H	CH_3—	H		(82)
4-$(NO_2)C_6H_4SO_2$—	H	C_6H_5—	H		(82)
4-$(NO_2)C_6H_4SO_2$—	H	C_4H_9—	H		(82)
4-$(NO_2)C_6H_4SO_2$—	H	CH_3—	CH_3—		(82)
4-$(NO_2)C_6H_4SO_2$—	H	$HOOCCH_2$—	H		(82)
4-$(NO_2)C_6H_4SO_2$—	H	HO_3SCH_2—	H		(82)
4-$(CH_3)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—	+	(37)
4-$(CH_3)C_6H_4SO_2$—	H	4-[4′-$(CH_3)C_6H_4SO_2NH$]C_6H_4—	H	0	(42)
3-HOOC-4-$ClC_6H_3SO_2$—	H	C_2H_5—	C_2H_5—		(44)
4-$(HOOC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(ClOC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(NH_2OC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(N_3OC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(NH_2NHOC)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)

3,4-$(CH_3O)_2C_6H_3SO_2$—	H	CH_3—	H		(90)
3,4-$(CH_3O)_2C_6H_3SO_2$—	H	CH_3—	CH_3—		(90)
3-$(NH_2)C_6H_4SO_2$—	H	3-$(NH_2)C_6H_4SO_2$—	Na—	+	(39)
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	H	++	(48, 90)
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	CH_3—*	++, +	(25, 26, 48, 90, 121, 140, 164)
4-$(NH_2)C_6H_4SO_2$—	K—	CH_3—	CH_3—	++	(48)
4-$(NH_2)C_6H_4SO_2$—	Na—	CH_3—	CH_3—	++	(48)
4-$(NH_2)C_6H_4SO_2$—	H	C_2H_5—	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H, Na— or K—	C_2H_5—	C_2H_5—		(25, 26, 90)
4-$(NH_2)C_6H_4SO_2$—	H	C_4H_9—	H		(90)
4-$(NH_2)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	H	++, 0	(9, 11, 37, 54, 90)
4-$(NH_2)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	CH_3—	++	(40)
4-$(NH_2)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—	+	(39, 90)
4-$(NH_2)C_6H_4SO_2$—	H	$CH_3CHOHCH_2$—	H	+, 0	(2, 39)
4-$(NH_2)C_6H_4SO_2$—	H	$(CH_3)_2C(OH)CH_2$—	H	0, ±	(2, 121)
4-$(NH_2)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	C_6H_5—	++	(39)
4-$(NH_2)C_6H_4SO_2$—	H	$HOOCCH_2$—	H	±	(9, 11, 90)
4-$(NH_2)C_6H_4SO_2$—	H	2-$(HOOC)C_6H_4$—	H	++	(39)
4-$(NH_2)C_6H_4SO_2$—	H	4-$(HOOC)C_6H_4$—	H		(123)
4-$(NH_2)C_6H_4SO_2$—	H	2-$(NaO_3S)C_6H_4$—	H		(23)
4-$(NH_2)C_6H_4SO_2$—	H	4-$(NaO_3S)C_6H_4$—	H	+	(39)
4-$(NH_2)C_6H_4SO_2$—	H	3,6,8-$(HO_3S)_3C_{10}H_4$—	H		(123)
4-$(NH_2)C_6H_4SO_2$—	H	4-[4′-$(NH_2)C_6H_4SO_2NH$]-1-NaO_3S-2-C_6H_3—	H	0	(42)
4-$(NH_2)C_6H_4SO_2$—	H	4-[4′-$(NH_2)C_6H_4SO_2NH$]$C_6H_4SO_2$-$NHCH_2CH_2$—	H	0	(42)
4-$(NH_2)C_6H_4SO_2$—	H	Morpholide		±	(121)
4-$(NH_2)C_6H_4SO_2$—	H	4-$(HO)C_6H_4SO_2$—	H		(42)

* Uleron.

TABLE 53—*Continued*

R^4	$R^{4\prime}$	R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
2. *N*⁴-Isocylic-sulfonyl—*Continued*					
4-$(NH_2)C_6H_4SO_2$—	H	4-$(NH_2)C_6H_4SO_2$—	H	+	(39)
4-$(NH_2)C_6H_4SO_2$—	Na—	4-[4′-$(NH_2)C_6H_4SO_2\underset{\displaystyle Na}{\underset{\vert}{N}}]C_6H_4SO_2$—	Na—	0	(39)
4-$[(CH_3)_2N]C_6H_4SO_2$—	H	CH_3—	CH_3—	++	(90)
4-$(HO_3SCH_2NH)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	CH_3—			(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90, 164)
4-$(CH_3CONH)C_6H_4SO_2$—	H	C_2H_5—	H		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	C_4H_9—	H		(90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	$HOCH_2CH_2$—	H		(9, 39, 90)
4-$(CH_3CONH)C_6H_4SO_2$—	H	$CH_3CHOHCH_2$—	H	0	(2)
4-$(CH_3CONH)C_6H_4SO_2$—	H	$(CH_3)_2COHCH_2$—	H	0	(2)
4-$(CH_3CONH)C_6H_4SO_2$—	H	$HOOCCH_2$—	H		(9)
4-$(CH_3CONH)C_6H_4SO_2$—	H	Morpholide		0	(121)
4-$(CH_3CONH)C_6H_4SO_2$—	H	 $C_2H_5OOCN\left\langle\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}\right\rangle N$—			(98)
4-$(CH_3CONH)C_6H_4SO_2$—	H	4-$(CH_3CONH)C_6H_4SO_2$—	H		(151)
4-$[CH_3(CH_2)_2CONH]C_6H_4SO_2$—	H	Morpholide		0	(121)
4-$[(CH_3)_2NCH_2CONH]C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-$(C_4H_9NHCH_2CONH)C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
 4-[HOOC NHSO$_2$ NHSO$_2$ NHCONH]- $C_6H_4SO_2$—	H	4-$(HOOC)C_6H_4$—	H		(123)
4-[4′-$(NH_2)C_6H_4SO_2NH]C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)

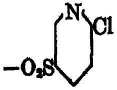
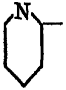
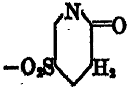
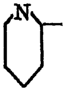
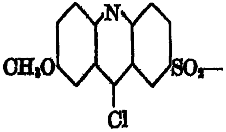
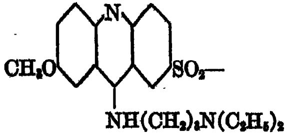
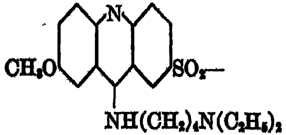
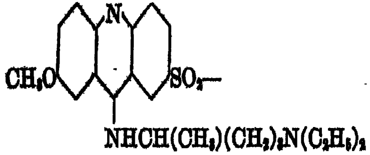
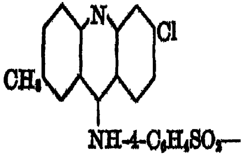
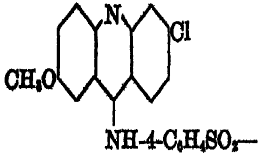
4-[4'-$(NH_2)C_6H_4SO_2NH$]$C_6H_4SO_2$—	H	$HOCH_2CH_2$—	H	±	(39)
4-[4'-$(NH_2)C_6H_4SO_2NH$]$C_6H_4SO_2$—	H	$HOCH_2CH_2$—	$HOCH_2CH_2$—	±	(39)
4-[4'-$(NH_2)C_6H_4SO_2NH$]$C_6H_4SO_2$—	H	4-$(NaO_3S)C_6H_4$—	H	++	(39)
4-[4'-$(CH_3CONH)C_6H_4SO_2NH$]$C_6H_4SO_2$—	H	CH_3—	CH_3—		(90)
4-[4'-$(CH_3O)C_6H_4NH$]-3-$(HOOC)C_6H_3SO_2$—	H	C_2H_5—	C_2H_5—		(44)
3. *N*⁴-Heterocyclic-sulfonyl					
	H		H		(150)
	H		H		(150)
	H	C_2H_5—	C_2H_5—		(44)
	H	C_2H_5—	C_2H_5—		(44)
	H	C_2H_5—	C_2H_5—		(44)

TABLE 53—*Concluded*

R^4	$R^{4\prime}$	R^1	$R^{1\prime}$	ACTIVITY	REFERENCES
3. *N*^{4}-Heterocyclic-sulfonyl—*Continued*					
	H	C_2H_5—	C_2H_5—		(44)
	H	C_2H_5—	C_2H_5—		(44)
	H	C_2H_5—	C_2H_5—		(44)

It is interesting also that 2-(N^4-benzylidinesulfanilamido)pyridine and 2-(N^4-3-hydroxybenzylidinesulfanilamido)pyridine were rated +++ against streptococci, but only + against pneumococci, whereas the corresponding N^4-(4-methoxybenzylidine) and N^4-(4-dimethylaminobenzylidine) derivatives were rated + against streptococci and + against pneumococci (102). If confirmed by other laboratories, results such as these would refute the argument that the activity of such derivatives can be explained by *in vivo* cleavage to sulfapyridine (which was rated ++ against both organisms), since obviously sulfapyridine, if the active agent, should not give *increased* activity against streptococci and *decreased* activity against pneumococci when administered as compounds which liberate it in the body. It would be interesting to see these results compared in terms of S.B.C.$_{50}$'s.

(*H*) *N^4-Azo-N^1-substituted sulfanilamides*

The N^4-azo-N^1-substituted sulfanilamides are listed in table 55.

VII. NUCLEAR,N^1,N^4-SUBSTITUTED SULFANILAMIDES

These compounds (see table 56) have been synthesized for other purposes usually, and only one has been tested for chemotherapeutic activity. It was inactive, which is not surprising in view of the usual effect of nuclear and N^4-substitution. The series of N^4-arylsulfanilamides was synthesized as intermediates for acridine derivatives of interest against malaria (see section IX).

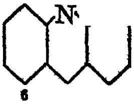
VIII. SALTS OF SULFANILAMIDE

Sulfanilamide, being an amphoteric substance, forms salts with both strong acids and bases (see table 57). The salts with bases hydrolyze in water to give pH values of 10 to 11, while the salts with acids give values of 2 to 3. The salt with 10-camphorsulfonic acid appears equal to sulfanilamide in effectiveness and has the advantage of being highly soluble so that it can be injected intravenously.

Greater effectiveness is claimed for complex salts of sulfanilamide with the cinchona alkaloids and halogen acids (176).

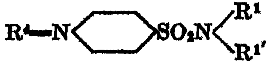
IX. UNCLASSIFIED SULFANILAMIDE DERIVATIVES

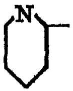
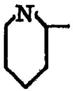
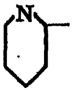
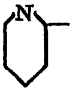
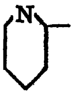
These derivatives are given in tables 58 and 59. In the case of the 2-acridinesulfonamides the numbering system used abroad is as follows:



54

N^4-Anil-N^1-substituted sulfanilamides



R^4	R^1	$R^{1'}$	ACTIVITY	REFERENCES
	(1) N^4-Acyclic-anil			
Dextrose		H	++	(161)
Galactose		H	+	(161)
	(2) N^4-Isocyclic-anil			
$C_6H_5CH=$	C_6H_5-	H	+, ±	(101, 102)
$C_6H_5CH=$	$4\text{-}(NO_2)C_6H_4-$	H	++, +++	(101, 102)
$C_6H_5CH=$		H	++, +++	(101, 102)
$C_6H_5CH=CHCH=$		H	++	(102, 169)
$2\text{-}(NO_2)C_6H_4CH=$		H	+++	(102)

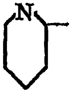
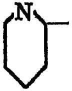
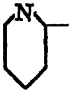
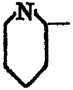
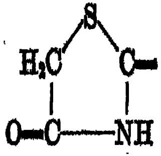
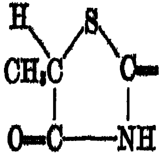
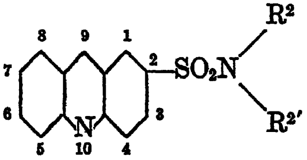
4-$(NO_2)C_6H_4CH=$	CH_3—	CH_3—		(90)
4-$(NO_2)C_6H_4CH=$	4-$(NO_2)C_6H_4$—	H	+	(102)
4-$(NO_2)C_6H_4CH=$	$HOOCC_6H_4$—	H		(91)
4-$(NO_2)C_6H_4CH=$	4-[4'-$(NO_2)C_6H_4CH{=}N]C_6H_4$—	H	±	(102)
4-$(NO_2)C_6H_4CH=$		H	+++	(102)
3-$(HO)C_6H_4CH=$		H	+++	(102)
4-$(CH_3O)C_6H_4CH=$	C_6H_5—	H	+	(101)
4-$(CH_3O)C_6H_4CH=$	4-$(NO_2)C_6H_4$—	H	+	(101)
4-$(CH_3O)C_6H_4CH=$		H	++, +	(101, 102)
4-$(CH_3O)C_6H_4CH=$	4-[4'-$(CH_3O)C_6H_4CH{=}N]C_6H_4$—	H	++	(102)
4-$[(CH_3)_2N]C_6H_4CH=$	C_6H_5—	H	+	(101)
4-$[(CH_3)_2N]C_6H_4CH=$	4-$(NO_2)C_6H_4$—	H	+	(101)
4-$[(CH_3)_2N]C_6H_4CH=$		H	+	(101)
4-$[(CH_3)_2N]C_6H_4CH=$	4-[4'-$[(CH_3)_2N]C_6H_4CH{=}N]C_6H_4$—	H	++	(102)

TABLE 54—*Concluded*

R^4	R^1	$R^{1'}$	ACTIVITY	REFERENCES
(8) *N*4-Heterocyclic-anil				
	$CH_3CHOHCH_2$—	H	0	(1)
	$CH_3CHOHCH_2$—	H	0	(1)

This numbering has been transcribed to the system used in *Chemical Abstracts* indices



(but not always in *Chemical Abstracts* text!).

E. SUMMARY AND GENERAL CONCLUSIONS ON CORRELATION OF STRUCTURE AND CHEMOTHERAPEUTIC ACTIVITY

The following conclusions are based on such scanty and variable pharmacological data that they are of little scientific value. They are given in the hope that they may guide future research to new achievements and that any negative conclusions will not discourage further work in that field.

I. SULFANILAMIDE DERIVATIVES

1. Nuclear-substituted sulfanilamides are usually inactive.

2. N^1-Substitution in sulfanilamide has given the most promising new derivatives.

(*a*) The N^1-acyclic derivatives have not been so active as the parent sulfanilamide.

(*b*) N^1-Arylsulfanilamides are in general not so active as sulfanilamide. Isomerism of substituents on the N^1-aryl nucleus has an important effect on activity.

(*c*) N^1-Heterocyclicsulfanilamides have shown great activity against pneumococci and equal or better activity against streptococci than sulfanilamide. Substituents on the heterocyclic ring modify the activity and position isomerism of such substituents may have a profound influence on the activity, which is difficult to explain in terms of current theories on the mode of action of sulfanilamide and its derivatives.

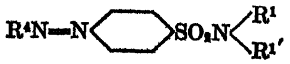
(*d*) Some N^1-acylsulfanilamides show activities somewhat greater than sulfanilamide on an equimolecular dosage. Branched-chain N^1-acylsulfanilamides are much less active than straight-chain derivatives.

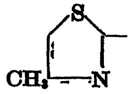
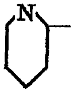
(*e*) N^1-Sulfonylsulfanilamides are generally inactive.

3. An hypothesis which needs verification by extensive pharmacological study is: *Blocking the N^4-nitrogen in sulfanilamide by a group which is not removed in vivo destroys the activity.* Groups which destroy the activity are alkyl, aryl, or sulfonyl. Groups which may be removed or converted *in vivo* to the free amine (or an active substance derived from the free

TABLE 55

N^4-Azo-N^1-substituted sulfanilamides



R^4	R^1	$R^{1'}$	ACTIVITY	REFERENCES
	(1) *N^4*-Acyclic-azo			
$CH_3CO(HOOC)CH—$	$4\text{-}[(CH_3)_2NSO_2]C_6H_4—$	H		(148)
	(2) *N^4*-Isocyclic-azo			
$C_6H_5—$	$Cl—$	$Na—$		(30, 175)
$C_6H_5—$	$Cl—$	$Cl—$		(30)
$C_6H_5—$	$Br—$	$Na—$		(31)
$C_6H_5—$	$Br—$	$K—$		(31)
$C_6H_5—$	$CH_3—$	$CH_3—$		(91)
$C_6H_5—$	$C_2H_5—$	H		(91)
$C_6H_5—$	$4\text{-}(HOOC)C_6H_4—$	H		(91)
$C_6H_5—$	$3\text{-}CH_3\text{-}4\text{-}(HO_3S)C_6H_3—$	H		(91)
$C_6H_5—$		H		(133)
$2,4\text{-}(HO)_2C_6H_3—$	$C_2H_5—$	$C_2H_5—$	+	(181)
$4,6\text{-}(HO)_2\text{-}2\text{-}(C_6H_{11})C_6H_2—$	$C_2H_5—$	$C_2H_5—$	±	(181)
$4\text{-}[Na(Cl)NSO_2]C_6H_4—$	$Na—$	$Cl—$		(175)
$4\text{-}[(C_2H_5)_2N]C_6H_4—$		H		(132)

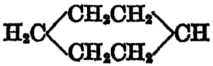
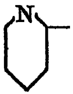
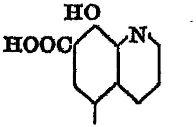
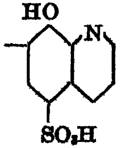
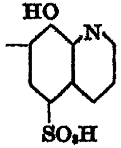
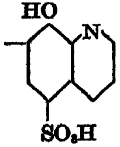
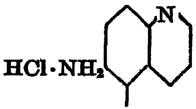
2,4-$(NH_2)_2C_6H_3$—	CH_3—	H		(86)
2,4-$(NH_2)_2C_6H_3$—	C_2H_5—	H		(86)
2,4-$(NH_2)_2C_6H_3$—	CH_3—	CH_3—		(86)
2,4-$(NH_2)_2C_6H_3$—	C_2H_5—	C_2H_5—		(86)
2,4-$(NH_2)_2C_6H_3$—	CH_2OHCH_2—	H		(86)
2,4-$(NH_2)_2C_6H_3$—	 $H_2C\left\langle\begin{smallmatrix}CH_2CH_2\\CH_2CH_2\end{smallmatrix}\right\rangle CH$	H		(86)
2,4-$(NH_2)_2C_6H_3$—	$HOOCCH_2$—	H		(136)
2,4-$(NH_2)_2C_6H_3$—	$HOOC(CH_3)CH$—	H		(136)
2,4-$(NH_2)_2C_6H_3$—	$C_6H_5CH_2$—	H		(68, 86)
2,4-$(NH_2)_2C_6H_3$—	Piperidide			(68, 86)
2,4-$(NH_2)_2C_6H_3$—	4-$(HO)C_6H_4CH_2(HOOC)CH$—	H		(136)
2,4-$(NH_2)_2C_6H_3$—		H		(68)
4-$HOOCCH_2O$-2-$(NH_2)C_6H_3$—	CH_3—	CH_3—		(88)
6-NH_2-1-HO-3-NaO_3S-2-$C_{10}H_4$—	Piperidide			(68)
7-NH_2-1-HO-3-HO_3S-2-$C_{10}H_4$—	$HOOCCH_2$—	H		(136)
7-NH_2-1-HO-3-HO_3S-2-$C_{10}H_4$—	$HOOC(CH_3)CH$—	H		(136)
7-NH_2-1-HO-3-HO_3S-2-$C_{10}H_4$—	4-$(HO)C_6H_4CH_2(HOOC)CH$—	H		(136)
2-$(C_2H_5)_2N$-5-HO-7-$(HO_3S)C_{10}H_4$—	CH_3—	CH_3—		(88)
1-$HOCH_2CH_2NH$-8-HO-3,6-$(HO_3S)_2C_{10}H_3$—	C_2H_5—	C_2H_5—		(88)
1-$HOCH_2CH_2NH$-8-HO-3,6-$(HO_3S)_2C_{10}H_3$—	Piperidide			(88)
1-$HOCH_2CH_2NH$-8-HO-3,6-$(HO_3S)_2C_{10}H_3$—	Pyrrolidide			(88)

TABLE 55—*Concluded*

R^4	R^1	$R^{1'}$	ACTIVITY	REFERENCES
(8) N^4-Heterocyclic-azo				
	C_2H_5—	H		(88)
	CH_3—	CH_3—		(88)
	C_4H_9—	H		(88)
	Piperidide			(88)
	CH_3—	CH_3—		(87)

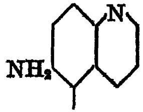
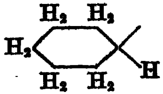
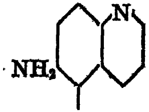
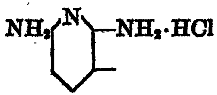
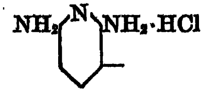
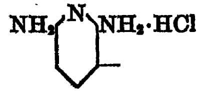
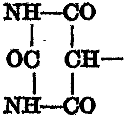
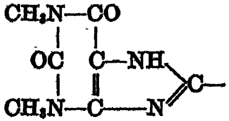
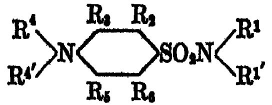
		H		(87)
	Piperidide			(87)
	$CH_3—$	H		(87)
	$CH_3—$	$CH_3—$		(87)
	$HOCH_2CH_2—$	$HOCH_2CH_2—$		(87)
	$4\text{-}[(CH_3)_2NSO_2]C_6H_4—$	H		(148)
	$4\text{-}[(CH_3)_2NSO_2]C_6H_4—$	H		(137)

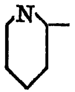
TABLE 56

Nuclear,N^1,N^4-substituted sulfanilamides



R^4	$R^{4\prime}$	R^1	$R^{1\prime}$	R_2	R_3	R_5	R_6	ACTIVITY	REFERENCES
A. N^4-Inorganic									
None									
B. N^4-Acyclic									
None									
C. N^4-Isocyclic									
C_6H_5—	H	C_6H_5—	H	H	NO_2—	H	H		(55)
C_6H_5—	H	C_6H_5—	H	H	NH_2—	H	H		(55)
C_6H_5—	H	C_6H_5—	H	H	$C_6H_5NHSO_2$—	H	H		(55)
3-$(CH_3)C_6H_4$—	H	CH_3—	CH_3—	H	HOOC—	H	H		(92)
4-$(CH_3)C_6H_4$—	H	CH_3—	CH_3—	H	HOOC—	H	H		(92)
4-$(CH_3O)C_6H_4$—	H	CH_3—	CH_3—	H	HOOC—	H	H		(92)
4-$(CH_3O)C_6H_4$—	H	C_2H_5—	C_2H_5—	H	HOOC—	H	H		(7, 92)
4-$(CH_3O)C_6H_4$—	H	CH_3—	CH_3—	H	Cl—	H	H		(92)
4-$(CH_3O)C_6H_4$—	H	CH_3—	CH_3—	H	CH_2CH_2NHCO— | $N(C_2H_5)_2$	H	H		(92)
4-$(CH_3O)C_6H_4$—	H	C_6H_5—	H	H	HOOC—	H	H		(7)

E. N^4-Acyl

CH_3CO—	H	$HO(CH_2)_4$—	H	H	CH_3O—	H	H	0	(121)
CH_3CO—	H		H	H	NO_2—	H	H		(98)
NH_2CO—	H	C_2H_5—	C_2H_5—	CH_3—	H	H	H	0	(34)
NH_2CO—	H	C_2H_5—	C_2H_5—	H	CH_3—	H	H	0	(34)
4-$(NO_2)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—	H	HOOC—	H	H		
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	CH_3—	H	HOOC—	H	H		
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	CH_3—	H	NaOOC—	H	H		
4-$(NH_2)C_6H_4SO_2$—	H	CH_3—	CH_3—	H	$(C_2H_5)_2NH \cdot HOOC$—	H	H		
4-$(NH_2)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—	H	HOOC—	H	H		
$(NH_2)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—	H	NaOOC—	H	H		
$(NH_2)C_6H_4SO_2$—	H	C_2H_5—	C_2H_5—	H	$(HOCH_2CH_2)_2NH \cdot HOOC$—	H	H		

Salts of sulfanilamide

A. Salts with acids

		ACTIVITY	REFERENCES
Inorganic acids......	Hydrochloride	++, +	(67, 86, 121)
	Phosphate		(192)
Acyclic acids........	Adipate		(61)
Isocyclic acids.......	Camphorate		(50)
	10-Camphorsulfonate	++	(53, 147, 170)
	Benzenesulfonate	++	(53, 170)
	Phenolsulfonate	++	(53, 170)
	Sulfosalicylate	++	(53, 170)
	Salicylate		(192)
	Acetylsalicylate		(192)
	Phenylglycolate		(192)
	Picrate		(168)
Heterocyclic acids...	Quinolinate		(50)
	3-Pyridinesulfonate		(50)
	8-Hydroxyquinolinesulfonate		(192)

B. Salts with bases

		ACTIVITY	REFERENCES
Inorganic bases......	Aluminum	+	(71)
	Mercuric Silver		
	Sodium	++	(42, 121)
Acyclic bases........	None		
Isocyclic bases......	Phenylmercuric		(110)
	Diphenylmercuric		(110)
Heterocyclic bases...	None		

C. Mixed salts

	ACTIVITY	REFERENCES
Quinine-sulfanilamide·2HCl	+++	(117, 176)
Quinine-sulfanilamide·2HBr		(118, 176)
Quinine-sulfanilamide·2HI		(118, 176)
Quinidine-sulfanilamide·H_2SO_4		(118, 176)
Quinidine-sulfanilamide·2HCl		(118, 176)
Quinidine-sulfanilamide·2HBr		(118, 176)
Euquinine-sulfanilamide·H_2SO_4		(118, 176)
Euquinine-sulfanilamide·2HCl		(118, 176)
Euquinine-sulfanilamide·2HBr		(118, 176)
Cinchonine-sulfanilamide·H_2SO_4		(118, 176)
Cinchonine-sulfanilamide·2HCl		(118, 176)
Cinchonine-sulfanilamide·2HBr		(118, 176)
Cinchonidine-sulfanilamide·H_2SO_4		(118, 176)
Cinchonidine-sulfanilamide·2HCl		(118, 176)
Cinchonidine-sulfanilamide·2HBr		(118, 176)
Quinine-sulfanilamide-salicylic acid	+++	(117, 176)
Quinine-sulfanilamide·H_2SO_4		(176)
Quinine-sulfanilamide·$1.5H_2SO_4$		(176)
Quinine-sulfanilamide·NH_2SO_3H		(176)
Quinine-sulfanilamide·4-[4′-$(NH_2)C_6H_4SO_2NH$]$C_6H_4SO_3H$		(176)

TABLE 58

Unclassified sulfanilamide derivatives

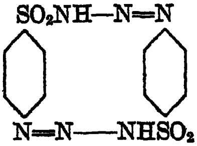
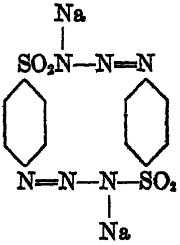
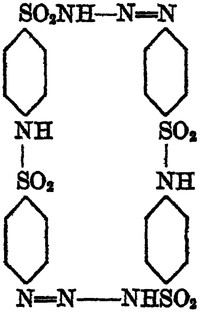
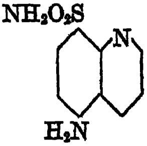
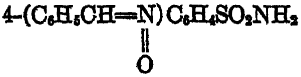
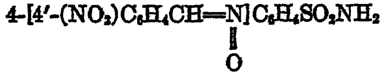
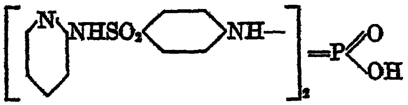
FORMULA	ACTIVITY	REFERENCES
	+	(115)
	+	(115)
	+	(115)
Various alkali, alkaline-earth, ammonium, and substituted ammonium salts of the above compounds are claimed		
4-[4′-$(NH_2SO_2)C_6H_4\ddot{N}{=}N]C_6H_4SO_2NH_2$		(16, 134)
		(165)
 $4\text{-}(C_6H_5CH{=}\underset{\underset{O}{\|}}{N})C_6H_4SO_2NH_2$		(135)

TABLE 58—*Concluded*

FORMULA	ACTIVITY	REFERENCES
 $4\text{-}[4'\text{-}(NO_2)C_6H_4CH{=}\underset{\underset{O}{\|}}{N}]C_6H_4SO_2NH_2$		(135)
	±	(179)

amine) are anils, certain reduced anils, formaldehyde-bisulfite, and formaldehyde-sulfoxalate derivatives.

4. N^1-Nuclear-, N^4-nuclear-, N^1,N^4-, and N^1,N^4,nuclear-substituted sulfanilamides follow in general the activities to be expected as a result of combining substituents on the basis of paragraphs 1, 2, and 3 above.

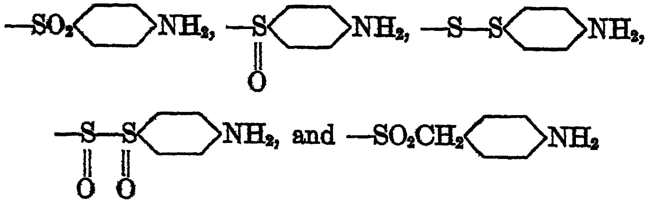
II. ALLIED COMPOUNDS

While not covered by this review, it may be worthwhile to summarize here the results to date on allied compounds. These results are based largely on work by the groups at The Pasteur Institute (61, 180, 181), Wellcome Research Laboratories (18, 19, 20, 69, 70), United States Public Health Service (9, 10, 11, 162, 198), and Rhône-Poulenc (134, 135, 195).

1. Isomers of sulfanilamide (metanilamide and orthanilamide) were inactive. Feinstone (54) has shown that this inactivity is intrinsic and not the result of a lack of adequate blood concentrations. Derivatives of these isomers were also inactive or nearly so.

2. Replacement of the amino group in sulfanilamide by H, —OH, —OR, —COOH, —SO_2NH_2, alkyl, or halogen practically destroyed the activity.

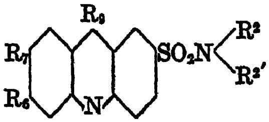
3. Replacement of the sulfonamido group by —NH_2, —CN, —SO_3H, —AsO_3H_2, —$CONH_2$, —$NHCOCH_3$, and —NO_2 destroyed the activity. Replacement by —SO_2H retained most of the activity (70). Replacement by



gave compounds of slight activity (62).

TABLE 59

2-Acridinesulfonamides



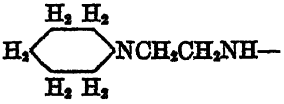
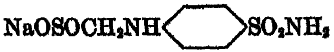
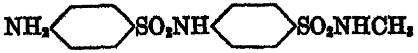
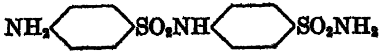
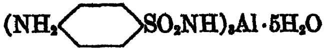
R^2	$R^{2\prime}$	R_6	R_7	R_9	REFERENCES
			CH_3O—	Cl—	(7)
			CH_3O—	$(C_2H_5)_2N(CH_2)_4NH$—	(7)
			CH_3O—	$(C_2H_5)_2N(CH_2)_3CH(CH_3)NH$—	(7)
CH_3—	CH_3—	CH_3—	H	Cl—	(92)
CH_3—	CH_3—	CH_3—	H	$(C_2H_5)_2NCH_2CHOHCH_2NH$—	(92)
CH_3—	CH_3—	H	CH_3—	Cl—	(92)
CH_3—	CH_3—	H	CH_3—	Br—	(92)
CH_3—	CH_3—	H	CH_3—	NaO_3S—	(92)
CH_3—	CH_3—	H	CH_3—	CH_3O—	(92)
CH_3—	CH_3—	H	CH_3—	C_6H_5O—	(92)
CH_3—	CH_3—	H	CH_3—	4-$(CH_3)C_6H_4S$—	(92)
CH_3—	CH_3—	H	CH_3—	$(C_2H_5)_2N(CH_2)_2S(CH_2)_3NH$—	(92)
CH_3—	CH_3—	H	CH_3—	4-$(NH_2CH_2)C_6H_4NH$—	(92)
CH_3—	CH_3—	H	CH_3—	4-$(CH_3CONHCH_2)C_6H_4NH$—	(92)
CH_3—	CH_3—	H	CH_3—	4-$(HOCH_2CH_2O)C_6H_4NH$—	(92)
CH_3—	CH_3—	H	CH_3—	4-$[(C_2H_5)_2NCH_2CH_2O]C_6H_4NH$—	(92)
CH_3—	CH_3—	H	CH_3—	 NCH_2CH_2NH—	(92)
CH_3—	CH_3—	H	CH_3O—	Cl—	(92)
CH_3—	CH_3—	H	CH_3O—	$(C_2H_5)_2N(CH_2)_5NH$—	(92)
CH_3—	CH_3—	H	CH_3O—	$(C_2H_5)_2NCH_2CHOHCH_2NH$—	(92)
CH_3—	CH_3—	H	CH_3O—	$(C_2H_5)_2NCH_2CHOHCH_2NHCH_2$- CH_2NH—	(92)
C_2H_5—	C_2H_5—	H	CH_3O—	Cl—	(7, 92)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2NCH_2CH_2NH$—	(92)
C_2H_5—	C_2H_5—	H	CH_3O—		(92)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2NCH_2CHOHCH_2NH$—	(92)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2NCH_2CH_2NH$—	(92)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2N(CH_2)_4NH$—	(7)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2N(CH_2)_3CH(CH_3)NH$—	(7)
C_2H_5—	C_2H_5—	H	CH_3O—	$(C_2H_5)_2NCH_2CHOHCH_2NH$—	(92)
C_6H_5—	H	H	CH_3O—	Cl—	(7)
C_6H_5—	H	H	CH_3O—	$(C_2H_5)_2N(CH_2)_4NH$—	(7)
C_6H_5—	H	H	CH_3O—	$(C_2H_5)_2N(CH_2)_3CH(CH_3)NH$—	(7)

TABLE 60

Trade names of sulfanilamide and derivatives

TRADE NAME	CHEMICAL NAME	FORMULA
Albucid	N^1-Acetylsulfanilamide	$4\text{-}(NH_2)C_6H_4SO_2NHCOCH_3$
Aldanil	Sodium formaldehyde-sulfoxalate derivative of sulfanilamide	
Azosulfamide	See Neoprontosil	
Coccoclase	See Sulfapyridine	
Colsulanyde	Sulfanilamide	
Dagenan	See Sulfapyridine	
Deseptyl	Sulfanilamide	
Diseptal A (DB90)	See Uleron	
Diseptal B (DB87)	N^1-Methyl-N^4-sulfanilylsulfanilamide	
Diseptal C	See Disulon	
Disulon	N^4-Sulfanilylsulfanilamide	
Estreptocida	Sulfanilamide	
Eubasinum	See Sulfapyridine	
Eubasin	See Sulfapyridine	
1162F	Sulfanilamide	
Lysamide	Aluminum sulfanilamide	
Lysococcine	Sulfanilamide	
M & B 693	See Sulfapyridine	

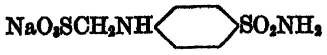
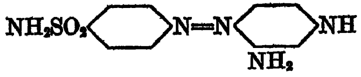
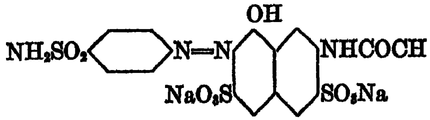
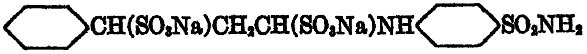
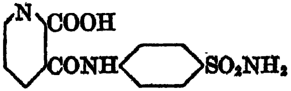
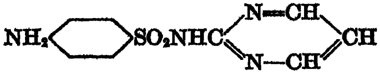
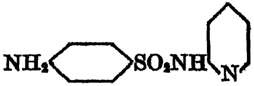
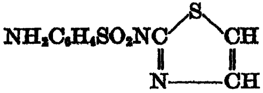
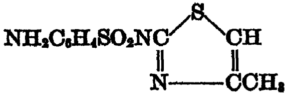
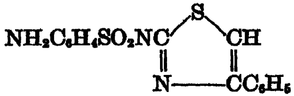
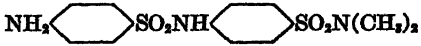
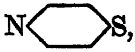
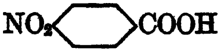
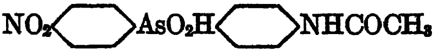
n	See Prontosil Soluble	
id	N^4-(Sodium sulfomethylene) sulfanilamide	
.tosil	2,4-Diaminoazobenzene-4′-sulfonamide	
Albur	Sulfanilamide	
Flavum	See Pron osil	
ontosil S oluble	Disodium 4-sulfamidophenyl-2-azo-7-acetylamino-1-hydroxynaphthalene-3,6-disulfonate	
Prontylin....	Sulfanilamide	
Proseptazine	See Septazine	
Pyriamid....	See Sulfapyric	
Rubi		
Sanamide................	Sulfanilamide	
Septazine (Setazine)......	N^4-Benzylsulfanilamide	$C_6H_5CHNHC_6H_4SO_2NH_2$
Septoplex...............	Sulfanilamide	
Soluseptazine............	N^4-(Disodium-α,γ-disulfo-γ-pheny propyl)sulfanilamide	
Stramide................	Sulfanilamide	
S tal Solubl		
S eptal	Sul	

TABLE 60—*Concluded*

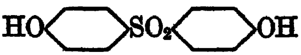
TRADE NAME	CHEMICAL NAME	FORMULA
Streptamid	Sulfanilamide	
Streptasol	*N*-Sulfanilylglycine	$NH_2C_6H_4SO_2NHCH_2COOH$
Streptocide	Sulfanilamide	
Streptocid Album	Sulfanilamide	
Streptocid Rubrum	See Neoprontosil	
Streptozon	See Prontosil	
Streptozon S	See Prontosil Soluble	
Sulfacet	See Albucid	
Sulfadiazine	2-Sulfanilamidopyrimidine	
Sulfamidyl	Sulfanilamide	
Sulfapyridine	2-Sulfanilamidopyridine	
Sulfathiazole	2-Sulfanilamidothiazole	
Sulfamethylthiazole	2-Sulfanilamido-4-methylthiazole	
Sulfaphenylthiazole	2-Sulfanilamido-4-phenylthiazole	
Sulphonamide P	Sulfanilamide	
Uleron (Uliron)	N^1,N^1-Dimethyl-N^4-sulfanilylsulfanilamide	

4. The fundamental unit common to the active compounds has been stated by Fourneau (62) to be , but the absolute need of both sulfur and nitrogen has been refuted by the finding of slight or moderate activity for the compounds


(195,198)


(196)

and


(194)

However, the latter compound has been called inactive by Buttle (70), so that it is uncertain whether nitrogen can be dispensed with.

F. Appendix A

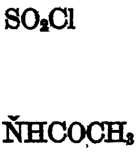
TRADE NAMES OF SULFANILAMIDE AND DERIVATIVES

Table 60 gives the trade names and formulas of sulfanilamide and its derivatives.

G. Appendix B

METHODS FOR SYNTHESIS OF SULFANILAMIDE DERIVATIVES

The common intermediate for almost all sulfanilamide derivatives is *N*-acetylsulfanilyl chloride (ASC):



This is obtained by the sulfonation of acetanilide with a 5-to-1 mole ratio of chlorosulfonic acid.[2] A wet paste of ASC results, which can be used for many purposes without drying or purification. When it is necessary to use purified ASC (as for reaction with expensive aminoheterocycles), it may be air-dried in thin layers on porous plates, or in a vacuum desiccator, and, when dry, recrystallized from a solvent. Benzene and ether, as described in the literature, are poor solvents. Much better results are obtained by using chloroform or ethylene dichloride.

N^4-Acetylsulfanilamide (ASA) is obtained by adding wet ASC to a large excess of 10 to 15 per cent ammonia at 40–50°C. with powerful agitation,

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[2] For its preparation see H. Gilman: *Organic Syntheses*, Collective Volume I, p. 8. John Wiley and Sons, Inc., New York (1932).

followed by neutralization of excess ammonia and filtration of the crude ASA. It may be purified by dissolving in warm sodium hydroxide solution, treatment with an activated charcoal, and reprecipitation with acid.

General methods for hydrolysis of N^4-acetylsulfanilamides

Sulfanilamide is obtained from ASA by hydrolysis of the acetyl group with either hydrochloric acid or sodium hydroxide. Contrary to the statement of Gelmo (66), sulfanilamide (and practically all of its N^1-derivatives with the exception of the N^1-acylsulfanilamides) is stable at the sulfonamide linkage to all concentrations of sodium hydroxide at temperatures up to 110°C. On the other hand, many of the N^1-heterocyclic derivatives of sulfanilamide are cleaved at this linkage by boiling hydrochloric acid. Practically all sulfonamide derivatives are cleaved by boiling with 65–70 per cent sulfuric acid. The choice of acid or alkaline hydrolysis is dictated by the nature of the compound. For one which is stable and soluble in acid, the acid hydrolysis is preferred, since it is complete in a few minutes, whereas the alkaline hydrolysis may take several hours.

Acid hydrolysis is generally carried out by boiling the compound with 15 to 20 per cent hydrochloric acid, using about 1.7 moles of the acid per amino equivalent. Hydrolysis is usually complete when the temperature has been at 100°C. for 30 min. The product is then precipitated by neutralization with sodium hydroxide.

Alkaline hydrolysis is preferred for sensitive compounds or compounds which are insoluble in acid. All sulfonamides having a hydrogen remaining on the amido nitrogen form highly water-soluble sodium salts. This is an aid in synthesis, not only in hydrolysis but also in purifications and studies of structure. Alkaline hydrolysis is usually carried out by dissolving the compound in 0.5 to 1.0 molar concentration in water by adding the necessary amount of sodium hydroxide. More sodium hydroxide (1.25 to 1.5 moles per equivalent of acetylamino groups) is then added, and the solution boiled until hydrolysis is complete (2 to 3 hr.), as determined by taking two aliquot samples, making strongly acid with hydrochloric acid, titrating one directly by nitrite (see below) and the other after boiling for 15 min. If the two nitrite values agree, hydrolysis is complete.

Synthesis of N^1-substituted sulfanilamides

If the N^1-substituent is acyclic or isocyclic, the usual method of synthesis is to dissolve or suspend the corresponding amine in water and to add ASC under vigorous agitation while maintaining a pH of 8 to 11 by addition of sodium hydroxide and holding the temperature at 40–50°C. It is convenient to use a little sodium carbonate as a buffer and indicator (when foaming starts additional sodium hydroxide is needed).

The crude N^4-acetyl-N^1-substituted sulfanilamide is obtained by acidifying and filtering. It may be purified by dissolving in alkaline solution and reprecipitating with acid after treatment with an activated charcoal, or by recrystallization from an organic solvent, of which alcohol is the most generally suitable.

Other methods of synthesis involve dry fusion of ASC with the base, or reaction in a mutual solvent such as acetone or dioxane. Use of pyridine as a solvent has definite advantages with a number of weak bases which do not react well with ASC in its absence. The ASC must be dried for such use, since it hydrolyzes rapidly in the presence of wet pyridine.

The N^4-acetyl group may be hydrolyzed by either of the general methods above, and the resulting N^1-substituted sulfanilamide purified by the same methods as used for the N^4-acetyl derivative. Advantage in purification may occasionally be taken of the ability of the free N^4-amino group to form soluble salts with acids. Since compounds with a free amino group are susceptible to oxidation, it is useful to add a small amount of a reducing agent, such as sodium bisulfite or sodium hydrosulfite, to help prevent such oxidation in the early stages of purification.

For synthesis of N^1-substituted sulfanilamides which are sensitive to hydrolysis by strong acids or bases, it is necessary to start with *p*-nitrobenzenesulfonyl chloride and to react this with the base by any of the above methods. The nitro group is then reduced by neutral iron reduction or catalytic hydrogenation. Unfortunately, there are no very satisfactory methods of preparing *p*-nitrobenzenesulfonyl chloride. The usual synthesis starts with *p*-nitrochlorobenzene, which is reacted with sodium disulfide in alcoholic solution to give 4,4′-dinitrodiphenyl disulfide. This is oxidized to the product with a mixture of nitric and hydrochloric acids or by chlorination in slightly diluted acetic acid. One of the essential points in this synthesis is to prepare pure sodium sulfide, sodium thiosulfate, etc.

Mention should also be made of the procedure of Bell (J. Chem. Soc. **1938**, Trans. 2776) for preparing *p*-nitrobenzenesulfonyl chloride.

Analysis

The diazotization of the amino group in sulfanilamide and its derivatives forms the basis for a volumetric method of assay which is also useful as a control test in following reactions. The method is as follows: Approximately 0.03 mole of the sample is weighed and dissolved (by warming if necessary) in 50 cc. of water and 15 cc. of concentrated hydrochloric acid. The solution is cooled to 15°C. by addition of ice and is then titrated with $N/10$ sodium nitrite solution (which has been standardized by an identical procedure using pure sulfanilic acid). The nitrite is added under constant agitation until the first *immediate* blue streak is obtained by drawing a stirring rod, wet with the solution, through a smear of starch–iodide paste on filter paper. This end point should be permanent for 2 min.

In cases where the compound is too insoluble to be titrated or where there is an N^4-acyl substituent, it is frequently possible to hydrolyze the sample to sulfanilic acid by boiling with 15 to 20 cc. of 65 per cent sulfuric acid for 30 min., then cooling with ice, adding 5 cc. of concentrated hydrochloric acid, and proceeding with the titration.

The starch–iodide paste may be prepared as follows: Dissolve 2 g. of potassium iodide in 10 cc. of water and add to 285 cc. of boiling water in a flask or beaker heated by an oil bath and mechanically agitated. Add a solution of 5 g. of C.P. zinc chloride in 20 cc. of water to the boiling mixture, then slowly add a suspension of 13 g. of potato starch in 60 cc. of cold water. Again raise to a boil, then allow to cool slowly. Preserve in well-stoppered bottles. The paste should give an *immediate* blue streak when tested with a solution of 1 cc. of $N/10$ sodium nitrite in 1 l. of water and 10 cc. of concentrated hydrochloric acid.

REFERENCES[3]

(1) ADAMS, R., LONG, P. H., AND JEANES, A.: J. Am. Chem. Soc. **61**, 2346 (1939).
(2) ADAMS, R., LONG, P. H., AND JOHANSON, A. J.: J. Am. Chem. Soc. **61**, 2342 (1939).

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[3] The following journals have been searched through the date of issue indicated:

Berichte der Deutschen Chemischen Gesellschaft	January, 1940
British Chemical Abstracts A, II, III	March, 1940
British Medical Journal	March 23, 1940
Chemical Abstracts, Sections 10, 11, 17	April 20, 1940
Helvetica Chimica Acta	February, 1940
Journal of the American Chemical Society	April, 1940
The Journal of the American Medical Association	March 30, 1940
Journal of the American Pharmaceutical Association	March, 1940
The Journal of Biological Chemistry	April, 1940
Journal of the Chemical Society (London)	January, 1940
The Journal of Pharmacology and Experimental Therapeutics	April, 1940
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ARTIFICIAL RADIOACTIVITY

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CONTENTS

I. INTRODUCTION

Artificial radioactivity was discovered by Curie and Joliot early in 1934 (C30). They made the exciting and important observation that the positrons which were emitted when aluminum was bombarded with alpha-particles from polonium continued to be emitted after the source of alpha-particles was removed. The intensity of positrons decayed exponentially with a half-life of about 3 min. Immediately following the discovery of Curie and Joliot, many more artificial radioactivities were produced by several groups of workers, mainly as the result of bombardment with high-speed charged particles from artificial sources. Many substances were rendered radioactive by bombardment with protons and deuterons which were accelerated in various types of high-voltage apparatus; Cockcroft, Gilbert, and Walton (C31) employed a voltage-multiplier circuit, Lawrence and coworkers (H32) accelerated the charged projectiles in the magnetic resonance accelerator or "cyclotron" (L33), Crane and Lauritsen (C32) used a "cascade transformer" potential source, and Tuve and Hafstad (H33) an electrostatic generator. A further large addition to the list of radioactivities was made during 1934 and 1935 as a result of the work of Fermi and his associates (A1), who produced the activities by the neutron bombardment of the elements. Since the Coulomb field of the nucleus does not oppose the entry of a neutron, as it does that of a charged particle, a large number of elements throughout the entire range of the Periodic Table were rendered radioactive in this manner.

By the end of 1935 about one hundred artificial radioelements were known, and a review of the subject of artificial radioactivity, which included a discussion of the methods of production, was published by Ridenour and Yost in *Chemical Reviews* (R18). In the meantime, further work with deuterons, neutrons, and protons, and in addition, high-energy alpha-particles and gamma-rays from artificial sources, made a large increase in the number of induced radioactivities. A number of tables of radioactivities have appeared in various physical journals (L34, D15, G10). Livingood and Seaborg have published, in the *Reviews of Modern Physics* (January, 1940), a table which describes the properties of three hundred and thirty artificial radioactivities (L35). These reviews in the physical journals merely listed the radioactivities and their properties and methods of production; they were not concerned with the applications of the radioelements to scientific problems.

The large currents and high energies now available, especially with the cyclotron, have resulted in the discovery of radioactive isotopes of every element in the range of atomic numbers from 1 to 85, inclusive (as well as thorium and uranium). Of especial importance, because of their wide applicability to tracer problems, are the radioactive hydrogen of Alvarez and Cornog (A7) and the long-lived radioactive carbon recently discovered by Ruben and Kamen (R17). It is the purpose of this review to discuss the present situation in the field of artificial radioactivity, particularly with respect to its applications to chemistry. Sections II to V will be devoted to a discussion of the properties and methods of production of the artificial radioelements and will include a brief description of the methods used for the detection of the radiations. Section VI gives a complete table (table 2) of all the known artificial radioelements, including their half-lives, the properties of their radiation, the reactions by which they are produced, and references to the original literature which describe their production. Section VII discusses the application of these radioelements to chemistry. The applications to chemistry that have been made so far are just the beginning of what is certain to become a very large and fruitful field of research.

II. GENERAL CONSIDERATIONS

The decay of the artificial radioelements follows, of course, the well-known exponential law, just as for the natural radioactive bodies, and the decay rate for each element is described in terms of a half-life.[1] Likewise the growth of a radioactivity when an element is under constant bombardment follows the familiar growth law, that is, the fraction of the saturation number of atoms formed in a time t is equal to $1 - e^{-\frac{0.69t}{T_{1/2}}}$, where $T_{1/2}$ is the half-life. After a time of activation long compared to the half-life of the substance, the activity reaches a saturation value which cannot be increased by further activation (see, e.g., R19, Chapter I).

Although the nomenclature for the artificial radioelements has not reached a standardized form, most of the investigators in the field have adopted the practice of using the contracted form "radioelement" rather than the more cumbersome term "radioactive element." For example, the well-known radioactivity of 14.8 hr. half-life induced in sodium, as the result of bombardment with either neutrons or deuterons, is often referred to as being due to *radiosodium* rather than the *radioactive isotope of sodium.* The former, simpler nomenclature will be used in this review.

The radiations from the artificial radioelements are very similar in properties to those from the natural radioelements of the well-known uranium, actinium, and thorium families (R19). Single decay predominates, although numerous examples of chain decays, i.e., cases where the product of the first decay is also radioactive, are known in artificial radioactivity. The beta-particles emitted during the decay of artificial radioactivities have the same continuous type of distribution in energy, with a definite upper energy limit, which has long been known to exist for the natural radioelements.[2] The upper energy limit decreases as the half-life increases; this Sargent (S35) relation (*log half-life* $\propto$ *−log energy*) holds only roughly over a range of mass values (B37) and must be modified when the nuclear spin change accompanying the disintegration is greater than zero (B37, F9). Decay by alpha-particle (He^{++}) emission, which occurs so often in natural radioactivity, is very uncommon in artificial radioactivity. While only negative beta-particles (electrons) are emitted

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[1] The half-life is the time required for one-half of the initial number of atoms to decay.

[2] It is this continuous distribution of beta-particle energy which has led to the introduction of the neutrino, a particle of small or zero mass, one-half unit of spin ($1/2 \cdot h/2\pi$) and no charge, in order to preserve the laws of conservation of energy and momentum in beta-decay (F9).

by natural radioelements, some of the artificial radioelements emit negative beta-particles and some of them emit positive beta-particles (positrons). Examples of radioelements which decay by the emission of both negative and positive beta-particles are known. Some of the decays are accompanied by gamma-rays (high-energy electromagnetic radiation) and some are not, just as in natural radioactivity, and these gamma-rays may be slightly or largely internally converted.[3] Gamma-rays ionize much less, and hence are much more penetrating, than beta-particles of similar energy.

Positron emitters may decay by the alternative process of orbital electron capture, a method of decay which, up to the present time, has been observed only with the artificial radioelements. It was suggested by Yukawa (Y3) and others, from considerations based upon the Fermi theory of beta-ray emission (F9), that an unstable nucleus might reach stability by the capture of an extranuclear electron. The first experimental observation of decay by "*K*-electron capture" (so-called because by far the largest proportion of the orbital electrons captured by the nucleus come from the *K*-electron shell) was made by Alvarez (A4), who found that an unstable gallium isotope of 83 hr. half-life decayed by this mechanism. Many examples of this type of decay are now known. Decay by *K*-electron capture may be unaccompanied by any detectable ionizing radiation except for the x-rays which must be emitted (since the vacant place in the inner shell must be filled with the emission of an x-ray or an Auger electron). However, many examples of *K*-electron capture are known where the resultant nucleus is left in an excited state which drops to the ground state with the emission of a gamma-ray or a line[4] of internal-conversion electrons or both. Some radioelements decay by both positron emission and *K*-electron capture, some by *K*-electron capture alone, and some entirely by positron emission.

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[3] When a gamma-ray is "internally converted" or undergoes "internal conversion," it means that instead of the emission of a gamma-ray there is the ejection of an electron from the extranuclear structure of the same atom that contains the nucleus which is radiating, the kinetic energy of the ejected electron being equal to the difference between the energy of the gamma-ray and the binding energy of the electron.

[4] The name "line of electrons" is often used to describe the *mono-energetic* electrons which are emitted from, for example, the *K*-electron shell, when gamma-rays undergo internal conversion. Some of the gamma-rays are converted in the *L*-, *M*-, etc. electron shells. The term "line" arises from the fact that with an electron magnetic spectrograph these groups of mono-energetic conversion electrons appear as lines on a photographic plate in contrast to the beta-particles from a beta-ray emitter, whose continuous distribution in energy darkens the plate over an entire, very broad, energy range.

Another class of radioactive substances, not peculiar to artificial radioactivity but most thoroughly studied here, are "nuclear isomers." Each member of a pair of nuclear isomers has the same atomic number and the same atomic weight (isotopic isobars); they represent two different energy states, the upper and the ground state, of the same nuclear species, differing in energy content and degree of stability. A theory which Weizsäcker (W21) has proposed in order to account for the existence of nuclear isomers ascribes the long lifetime of the upper, metastable state to a difference of several units of angular momentum between the metastable and ground state. This large spin difference forbids the transition from the upper to the lower state in a manner analogous to the forbidden transitions in optical spectra. Each isomer of a pair may be radioactive and decay by beta-emission with its own characteristic half-life, or the isomer corresponding to the upper energy state may be beta-active while that corresponding to the ground state may be stable. Some isomers are genetically related to each other; the upper state, rather than decaying by beta-particle emission to a neighboring isobar, decays by an *isomeric transition* to the ground state with the emission of a gamma-ray.[5] The first evidence for nuclear isomerism in artificial radioactivity was presented in 1935 by Kourtchatow and coworkers (K5), and in 1937 Snell (S9) and Bothe and Gentner (B28) simultaneously showed that an 18-min. period and a 4.4-hr. period must both be ascribed to a bromine isotope of atomic weight 80.

III. METHODS OF CHEMICAL IDENTIFICATION AND CONCENTRATION

The chemical identification of artificial radioelements is based on the fact that isotopes are not appreciably separated by ordinary chemical reactions and the radioactive isotopes of a given element behave in the same manner as the stable isotopes of the element. The property of radioactivity does not influence the chemical behavior (except in the case of extremely strong activities, and then in the same way as an external source would do). Thus, after a transmutation has taken place leading to the formation of a new and unstable nucleus, the new atom has properties determined solely by its new atomic number and will behave chemically in all respects like its stable isotope or isotopes. Often only a few millions of atoms of the unstable transmutation product are formed. The behavior of an element at such a low concentration may be uncertain in many chemical procedures. For this reason, in order to establish the chemical identity of the transmu-

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[5] The present theoretical explanation for the phenomenon of nuclear isomerism leads to the prediction that the gamma-rays corresponding to an isomeric transition will undergo high internal conversion when the energy is small,—of the order of tens of kilovolts (H45, D20).

tation product, it is usually expedient and often absolutely necessary to add a small quantity of that element which is isotopic with the expected or suspected transmutation product. This added material is usually designated by the term "carrier." The carrier element is separated out chemically and in this manner one can establish a radioactivity, with a characteristic half-life, which is isotopic with the carrier element.

In many cases, when the radioelement is not isotopic with the element from which it is formed, the radioactivity can be concentrated in a very small amount of material by adding and separating out only a very small amount of carrier. Such a high ratio of activity to carrier material (high *specific activity*) is very desirable in many of the investigations which employ radioelements, especially in biological chemistry and physiological and biological studies. The *specific activity* may be defined as the ratio of the number of radioactive atoms to the total number of isotopic atoms with which the radioactive atoms are mixed.

When the radioactivity is isotopic with the element which is bombarded, the active isotope is necessarily mixed with a larger quantity of its inactive isotopes. However, it is sometimes possible to effect a separation of the radioactive isotope from the inactive isotopes and hence a concentration of the radioactive isotope in a small amount of material. Szilard and Chalmers (S28) were the first to show that radioactive iodine could be separated from ordinary iodine after irradiating with neutrons a non-ionizing organic compound such as ethyl iodide. After the irradiation, a very small amount of free iodine was added to act as a carrier for the free radioactive iodine, and after this iodine was reduced and precipitated as silver iodide it was found to contain practically all of the radioactivity. This method of concentration, which has subsequently been used to concentrate a number of radioelements, is now known as the "Szilard–Chalmers method." Its success depends upon the removal of the newly formed radioactive nucleus from its chemical bond in the irradiated compound. The breaking of this bond is a result of the large amount of energy furnished by the recoil from the gamma-rays emitted during the neutron-capture process. The method is not limited to radioelements formed by irradiation with neutrons, but in principle can be applied to other methods of activation. It is, of course, essential that the radioactive atoms set free during the bombardment do not interchange with their isotopic atoms in the irradiated chemical compound. As examples of the application of this method, radioactive iodine, bromine, and chlorine can be concentrated, using either organic compounds or the inorganic halogenates. Similarly, manganese dioxide precipitated from an irradiated permanganate is found to carry most of the radiomanganese under certain conditions. Whenever it is desired to use this method in order to produce a radioactive isotope with a high specific activity, a search is made for a compound which contains the element in a form which will not interchange with the freed radioactive atoms and from which the radioactive atoms will be liberated during and separable after the irradiation process.

Erbacher and Philipp (E8), Lu and Sugden (L42), and Roginsky and Gopstein (R21) have developed a number of excellent methods for the extraction with high yields of very concentrated radioactive halogens from neutron-irradiated organic halides. One of the techniques employed by Erbacher and Philipp (E8) depended upon the absorption of the radioactive atoms on active charcoal, and Roginsky and Gopstein (R21) have used aluminum oxide and active charcoal as absorbents. Majer (M25, M31) has used a trace of colloidal gold to supply condensation nuclei for the deposition of active gold atoms formed in a neutron-irradiated, alkaline gold chloride solution.

A method for the chemical separation of genetically related nuclear isomers, which is a modification of the Szilard–Chalmers method, has been invented by Segrè, Halford, and Seaborg (S10). The element which contains the radioactivity corresponding to an upper isomeric energy state is made into a compound suitable for the application of the Szilard–Chalmers method of concentration; the daughter radioactivity, which corresponds to the ground state and which is liberated from this compound as a result of the isomeric transition,[6] is then chemically separable from the parent radioactivity. Segrè, Halford, and Seaborg (S10) used this method to extract the bromine radioactivity of 18 min. half-life, in the form of hydrobromic acid, from its parent isomer of 4.4 hr. half-life, which was present as tertiary butyl bromide. DeVault and Libby (D12) made the same separation by precipitating silver bromide from an ammoniacal solution which contained the 4.4-hr. radioactivity in the form of the bromate, while Le Roux, Lu, and Sugden (L36) separated the 18-min. radioactivity as silver bromide from both ethylene dibromide and *n*-butyl bromide. Seaborg, Livingood, and Kennedy (S15) have applied this isomer separation technique to tellurium to extract three daughter radioactivities from their three parent radioactivities, and Langsdorf and Segrè (L30) have separated a pair of isomers in selenium. A more complete discussion of the work which has been done on the Szilard–Chalmers and isomer separation methods appears in section VII.

In some cases when the transmutation product is not isotopic with the target element, it is possible to separate it from the target element without the use of carrier. This gives the pure radioactive element, or compound

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[6] The mechanism of the bond-rupture process, which seems to depend upon internal conversion of the transition gamma-ray, has been investigated in some detail and will be discussed in section VII.

of the element, in much too small an amount to be seen, detectable only by its radioactivity. A few examples will serve to illustrate the type of physical and chemical properties which may serve to make such a separation feasible.

Haissinsky (H34) separated pure radiocopper, produced by neutron bombardment of zinc, by means of electrochemical deposition on lead, while Steigman (S29) effected the same separation by electrolysis. Segrè (S30) found that the radiosodium present in a sample of magnesium hydroxide, after deuteron bombardment of the magnesium, could be dissolved out of the hydroxide quantitatively by treating it with water.

Partition between solvents affords another method for separating the radioactive isotope in its pure form in the absence of carrier material. Grahame and Seaborg (G11) have used the partition between ether and 6 *N* hydrochloric acid to separate pure radiogallium from zinc as well as radiomanganese and radiocobalt from iron.

When there exists a large difference in the boiling points, this may be used to effect a separation. For example, a gaseous, radioactive transmutation product can be easily separated from a non-gaseous target element or parent element. Alvarez, Helmholz, and Nelson (A12) have separated practically pure radiocadmium by collecting the vapor after heating deuteron-activated silver to its melting point.

When the radioactive transmutation product forms an extremely insoluble compound, it should be possible to collect the invisible precipitate on the walls of the containing vessel after centrifugation, as has been done for many of the naturally radioactive elements (H52, C36, H39).

Another method of separation depends on the fact that the newly formed radioactive atom may have lost one or more of its extranuclear electrons at the moment of formation as a result of the recoil given to it by the gamma-ray emitted during the capture process. The charged atoms formed in this manner may be collected, during the bombardment of either a gaseous or a liquid substance, with the aid of an electric field. This method of concentration, which is sometimes applicable even when the radioactive product is isotopic with the target element, has been employed by Fermi and his associates (A1) and by Paneth and Fay (P11) and Govaerts (G15). The collection of recoil radioactive atoms produced during bombardment with charged particles can also be used as a method for obtaining concentrated radioactive samples (S3).

Erbacher (E10) and Maier-Leibnitz (M30) have devised means to extract radioactive P^{32} of very high specific activity from carbon disulfide which has been bombarded with fast neutrons.

When the transmutation product is isotopic with an element of which no stable isotopes have been found in nature or which is very rare and not available for use as carrier for the radioactive isotopes, the matter of chemical separation becomes more difficult. For example, Perrier and Segrè (P12) found that the deuteron bombardment of molybdenum produced radioactive isotopes of element 43. Since no stable element 43 is available, the chemical identification was carried out with the aid of rhenium, an element in the same group of the Periodic Table, which was expected to have very similar chemical properties to element 43. Similarly, Corson, MacKenzie, and Segrè (C46, C23) were able, with the aid of iodine as a carrier, to identify as element 85 a radioactive transmutation product produced from bismuth plus 32-Mev. alpha-particles. McMillan and Abelson (M28) were able to show by means of a series of chemical experiments that one of the radioactivities formed when uranium is bombarded with neutrons must be ascribed to element 93.

IV. METHODS FOR DETECTION OF RADIATIONS

There are a number of different types of instruments that are used for the measurement of the intensity of the radiations from radioactive substances (L25). No attempt will be made to describe all of them, but some of those which are being used at present by workers in this field will be mentioned briefly. The best type of instrument for a given problem depends upon the type and energy of the radiation and upon the sensitivity and stability which is required. A knowledge of the absorption curve for the radiation to be measured is often very important, especially if the radiation is of very low energy (i.e., very soft), since this will make it necessary to pay particular attention to the effect of self-absorption in the sample and to use a detection device of the proper design.

One of the simplest instruments, widely used, is the Lauritsen modification of the electroscope, known as the "quartz-fiber electroscope" (L44). The electroscope is usually used inside an ionization chamber, which may be filled with any gas, although air is usually used for convenience, and the rate of drift of the fiber across a scale is measured. This instrument, which is suitable for the detection of all types of radiations from radioactive substances, is one compact unit and requires for its operation only a D.C. potential source of the order of 200 volts. Its sensitivity is not as large as that of some of the other detection devices. The quartz-fiber electroscope can be used to best advantage with a radioactivity whose intensity is of the order of microcuries (10^{-6} curies[7]), although intensities which are 1 per cent, or even 0.1 per cent, as strong as this can be measured.

A more sensitive arrangement of the integrating type, also suitable for

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[7] The "curie," originally the name for the amount of radon in equilibrium with 1 g. of radium, is now usually taken as the name for the general unit of intensity in radioactivity; a curie of any radioactive material undergoes the same number of disintegrations per unit time as 1 g. of radium, namely, 3.7×10^{10} disintegrations per second.

the detection of all types of radiation from radioactive substances, is obtained with an ionization chamber connected to some kind of an electrometer. Segrè (S44), Amaldi and Fermi (A13), Barnes (B29), and Montgomery and Montgomery (M33) have given descriptions of the construction of various types of ionization chambers. These chambers, which usually consist of an outer cylinder with a central, coaxial electrode, require 300 to 400 volts of D.C. potential for their operation and may be designed so as to contain any gas. The gas may be at atmospheric pressure, which is necessary when a thin window is used, or higher pressures may be used to increase the detection sensitivity for penetrating radiation such as gamma-rays. The measurement of extremely soft radiation can be accomplished by introducing the sample into the inside of the ionization chamber. Any sensitive electrometer can be used; both the Edelmann electrometer and the Perucca electrometer have been used in practice and found to be particularly satisfactory. Various vacuum-tube electrometer systems have been described by Hafstad (H35), DuBridge and Brown (D16), and Barth (B30). The ionization current is amplified by a single-tube D.C. amplifier and is read as a deflection on a sensitive galvanometer; a modification in which the "rate of drift" of the galvanometer current is read increases the sensitivity for the measurement of the radiations from weak samples (intensities of the order of 10^{-4} microcuries can be measured).

An ionization chamber of a different design can be used to detect single, heavily ionizing particles, such as protons, alpha-particles, etc., when connected to a high-gain, multiple-stage, A.C. (pulse) amplifier as described by Dunning (D17). Electrons and gamma-rays (which show themselves only by the electrons liberated from the material they pass through) are not recorded with this arrangement.

The most sensitive detection device is the Geiger counter (G12), also known as the "point" counter, an instrument which detects individual ionizing particles of all kinds. A modification of the original Geiger counter which is now widely used is the Geiger–Müller counter (G13), which is also known as the "tube" counter and the "Zählrohr." With this instrument it is possible to detect the ionizing particles from a source as weak as 10^{-5} microcuries. The Geiger–Müller counter consists of a cylinder and a coaxial wire which is insulated from the cylinder. It is filled with some gas such as air or argon at reduced pressure and is operated with a negative voltage of 500 to 5000 volts on the outer cylinder. The passage of an ionizing particle through the counter causes a temporary electrical breakdown between the outer cylinder and the central wire, and this pulse is usually amplified by an A.C. (pulse) amplifier to a stage where it is capable of operating a mechanical recorder in a recording circuit. In spite of the vast amount of research which has been done, it is felt by many that the construction and operation of the Geiger–Müller counter is still somewhat more of an art than a science. Neher (S31) gives an excellent description of the construction of several types of counters and of various vacuum-tube circuits for their operation. Hamblin and Johnson (H53) have also given a good discussion of counters and counting apparatus. Olson, Libby, Long, and Halford (O3) and Bale, Haven, and LeFevre (B47) have described Geiger–Müller counter arrangements which can be used to measure the radiations from radioactive substances in solution.

When the particle radiation from the radioactive element is of very low energy, the radioactive material, in the form of a gas, can be introduced into the interior of an ordinary ionization chamber (L30) or Geiger–Müller counter (R17, S33). An arrangement which allows a radioactive sample of solid material to be introduced into the interior of a counter, and which allows background counts to be made while such a sample is inside, is the "screen-wall" counter described by Libby (L50) and Libby and Lee (L51). Of course, when the low-energy particle radiation is accompanied by gamma-radiation it may not be necessary to introduce the sample into the interior of the counter or ionization chamber. However, the lower efficiency of gamma-ray detection makes it necessary to have strong samples for measurements which depend entirely upon gamma-radiation.

The "proportional" counter, first described by Geiger and Klemperer (G14), is a modification of the Geiger and the Geiger–Müller counter which is operated at a lower voltage (and with a higher gain pulse amplifier), so that only heavily ionizing particles such as protons, alpha-particles, etc., are detected. A description of this type of counter arrangement, which does not respond to electrons and gamma-rays, has been given by Brubaker and Pollard (B31).

For most work involving the use of the radioelements as indicators the choice of detection device will be made from the following group: (*1*) electroscope, (*2*) Geiger–Müller counter, or (*3*) integrating ionization chamber.[8] These instruments can be used to obtain absorption curves

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[8] Only a very rough comparison of the costs of the above instruments can be made. An ordinary Lauritsen electroscope can be purchased as a single unit (excluding batteries) for about forty-five dollars from the F. C. Hensen Company, 3311 E. Colorado Street, Pasadena, California. Geiger–Müller counter equipment is also available commercially. Geiger–Müller counter tubes, of various designs, can be purchased for twenty-five to thirty dollars each from the W. M. Welch Scientific Company, 1515 Sedgwick Street, Chicago, Illinois, and at a price of about ten to twenty dollars each from Herbach and Rademan, Inc., 522 Market Street, Philadelphia, Pennsylvania. The latter company also sells all the assembled auxiliary equipment necessary for the operation of a Geiger–Müller counter, at a price ranging from one hundred to one hundred fifty dollars. Although the construction cost of an

in order to determine the energy of radiations from radioactive substances. The upper energy limits of beta-particles are usually determined with the help of the relationship of Feather (F13), $R = 0.543E - 0.160$, where R is the range in grams per cm.^{2} of aluminum and E is the energy in Mev. (good only for $E > 0.6$ Mev.), while for gamma-rays the correlation of energy with absorption coefficient as listed in the table compiled by Gentner (G17) can be conveniently used.

Brief mention should also be made of other experimental arrangements which are used primarily for detailed studies of the properties and energy of radiations. The spectrograph or spectrometer (E11, L54) uses a magnetic or electric field to bend, to an extent dependent upon their energy, the beta-particles, the internal-conversion electrons, or the secondary electrons from gamma-rays. The particles are detected either by a photographic method or by a counter or ionization chamber. Another arrangement involves two or more counters connected to an amplifier of a type which records the counts only when the counters discharge simultaneously (B38). This "coincidence counter" arrangement is often used to determine the energy of gamma-rays by determining the absorption curve of the secondary electrons which are producing the coincidence counts. A complete discussion of the theory and practice of coincidence counting has been given by Dunworth (D23). Finally, there is the expansion chamber or cloud chamber of Wilson (W17) (usually used with a magnetic field), in which can be seen and photographed the water drops which condense along the path of an ionizing particle.

Another instrument which should be mentioned is the secondary electron multiplier tube as adapted to counting purposes by Allen (A15). This device, which detects single positive ions, electrons, and photons by producing a large current of secondary electrons inside a single vacuum tube, is most useful for special problems in physics where work in a vacuum and an extremely low background (< one count per minute) are paramount factors.

V. TYPES OF REACTIONS AND METHODS OF PRODUCTION

Table 1 presents a list of the known stable isotopes together with their relative abundances.[9] (The more abundant natural radioelements, marked with the sign †, are included.) All of the artificial radioelements

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integrating ionization chamber will depend largely on the facilities available, the total price of such a chamber and good auxiliary equipment will probably amount to two hundred dollars or more.

[9] This table is taken from the article of Livingood and Seaborg (L35). Attention is called to the very complete review article on the stable isotopes recently published by Hahn, Flügge, and Mattauch (H36). This includes exact mass and packing fraction values obtained from both mass spectrographic and transmutation data.

TABLE 1

Stable isotopes of the elements

Z	ELEMENT	A	PER CENT ABUNDANCE
1	H	1	99.98
		2	0.02
2	He	3	$\sim10^{-5}$
		4	100
3	Li	6	7.9
		7	92.1
4	Be	9	100
5	B	10	18.4
		11	81.6
6	C	12	98.9
		13	1.1
7	N	14	99.62
		15	0.38
8	O	16	99.76
		17	0.04
		18	0.20
9	F	19	100
10	Ne	20	90.00
		21	0.27
		22	9.73
11	Na	23	100
12	Mg	24	77.4
		25	11.5
		26	11.1
13	Al	27	100
14	Si	28	89.6
		29	6.2
		30	4.2
15	P	31	100
16	S	32	95.0
		33	0.74
		34	4.2
		36	0.016
17	Cl	35	75.4
		37	24.6
18	A	36	0.307
		38	0.061
		40	99.632
19	K	39	93.3
		40†	0.012
		41	6.7
20	Ca	40	96.96
		42	0.64
		43	0.15
		44	2.06
		46	0.0033
		48	0.19
21	Sc	45	100
22	Ti	46	7.95
		47	7.75
		48	73.45
		49	5.51
		50	5.34
23	V	51	100
24	Cr	50	4.49
		52	83.77
		53	9.43
		54	2.30
25	Mn	55	100
26	Fe	54	6.04
		56	91.57
		57	2.11
		58	0.28

† Natural radioactivity.

TABLE 1—*Continued*

Z	ELEMENT	A	PER CENT ABUNDANCE
27	Co	57	0.17
		59	99.83
28	Ni	58	68.0
		60	27.2
		61	0.1
		62	3.8
		64	0.9
29	Cu	63	68
		65	32
30	Zn	64	50.9
		66	27.3
		67	3.9
		68	17.4
		70	0.5
31	Ga	69	61.2
		71	38.8
32	Ge	70	21.2
		72	27.3
		73	7.9
		74	37.1
		76	6.5
33	As	75	100
34	Se	74	0.9
		76	9.5
		77	8.3
		78	24.0
		80	48.0
		82	9.3
35	Br	79	50.6
		81	49.4
36	Kr	78	0.35
		80	2.01
		82	11.53
		83	11.53
		84	57.10
		86	17.47
37	Rb	85	72.3
		87†	27.7
38	Sr	84	0.56
		86	9.86
		87	7.02
		88	82.56
39	Y	89	100
40	Zr	90	48
		91	11.5
		92	22
		94	17
		96	1.5
41	Cb	93	100
42	Mo	92	15.5
		94	8.7
		95	16.3
		96	16.8
		97	8.7
		98	25.4
		100	8.6
44	Ru	96	5
		98	?
		99	12
		100	14
		101	22
		102	30
		104	17
45	Rh	101	0.08
		103	99.92
46	Pd	102	0.8
		104	9.3
		105	22.6
		106	27.2
		108	26.8
		110	13.5
47	Ag	107	52.5
		109	47.5

† Natural radioactivity.

TABLE 1—*Continued*

Z	ELEMENT	*A*	PER CENT ABUNDANCE
48	Cd	106	1.4
		108	1.0
		110	12.8
		111	13.0
		112	24.2
		113	12.3
		114	28.0
		116	7.3
49	In	113	4.5
		115	95.5
50	Sn	112	1.1
		114	0.8
		115	0.4
		116	15.5
		117	9.1
		118	22.5
		119	9.8
		120	28.5
		122	5.5
		124	6.8
51	Sb	121	56
		123	44
52	Te	120	<0.1
		122	2.9
		123	1.6
		124	4.5
		125	6.0
		126	19.0
		128	32.8
		130	33.1
53	I	127	100
54	Xe	124	0.094
		126	0.088
		128	1.90
		129	26.23
		130	4.07
		131	21.17
		132	26.96
		134	10.54
		136	8.95
55	Cs	133	100
56	Ba	130	0.101
		132	0.097
		134	2.42
		135	6.59
		136	7.81
		137	11.32
		138	71.66
57	La	139	100
58	Ce	136	<1
		138	<1
		140	90
		142	10
59	Pr	141	100
60	Nd	142	25.95
		143	13.0
		144	22.6
		145	9.2
		146	16.5
		148	6.8
		150	5.95
62	Sm	144	3
		147	17
		148†	14
		149	15
		150	5
		152	26
		154	20
63	Eu	151	49.1
		153	50.9
64	Gd	152	0.2
		154	1.5
		155	20.7
		156	22.6
		157	16.7
		158	22.6
		160	15.7

† Natural radioactivity.

TABLE 1—*Concluded*

Z	ELEMENT	*A*	PER CENT ABUNDANCE
65	Tb	159	100
66	Dy	158	0.1
		160	1.5
		161	21.6
		162	24.6
		163	24.6
		164	27.6
67	Ho	165	100
68	Er	162	0.25
		164	2.0
		166	35.2
		167	23.5
		168	29.3
		170	9.8
69	Tm	169	100
70	Yb	168	0.06
		170	2
		171	8.8
		172	23.5
		173	16.7
		174	37.2
		176	11.8
71	Lu	175	97.5
		176†	2.5
72	Hf	172?	<0.1
		174	0.3
		176	5
		177	19
		178	28
		179	18
		180	30
73	Ta	181	100
74	W	180	∼0.2
		182	22.6
		183	17.3
		184	30.1
		186	29.8
75	Re	185	38.2
		187	61.8
76	Os	184	0.018
		186	1.59
		187	1.64
		188	13.3
		189	16.1
		190	26.4
		192	41.0
77	Ir	191	38.5
		193	61.5
78	Pt	192	0.8
		194	30.2
		195	35.3
		196	26.6
		198	7.2
79	Au	197	100
80	Hg	196	0.15
		198	10.1
		199	17.0
		200	23.3
		201	13.2
		202	29.6
		204	6.7
81	Tl	203	29.1
		205	70.9
82	Pb	204	1.48
		206	23.59
		207	22.64
		208	52.29
83	Bi	209	100
90	Th	232†	100
91	Pa	231†	
92	U	234†	0.006
		235†	0.71
		238†	99.28

† Natural radioactivity.

are prepared from these isotopes with the help of various kinds of bombarding particles, such as neutrons, deuterons, alpha-particles (helium ions), protons, high-energy gamma-rays, and x-rays. The artificial radioelements with mass numbers smaller than those of the stable isotopes of the same element reach stability by the emission of positrons (or by *K*-electron capture); those with larger mass numbers attain stability by the emission of negative beta-particles. A radioelement whose mass number lies between the mass numbers of two stable isotopes is usually a negative beta-particle emitter.

In order to identify completely a radioactivity it is necessary to establish the mass number of the active isotope as well as the atomic number, which is identified by the chemical separations. The mass number of the radioactive isotope can be deduced sometimes from a study of the known mass numbers of the stable isotopes of the target element after the chemical separation has established the type of reaction; often the identification must be made by the method of "cross bombardment," i.e., the preparation of the radioactive isotope by several independent nuclear reactions. The bombardment of separated isotopes should offer a powerful method for the isotopic identification of induced radioactivities, in view of the excellent isotope separation methods which have been recently developed by Urey and associates (H46), by Clusius and Dickel (C34), and by Beams and associates (B42). For example, Kennedy and Seaborg (K18) bombarded separated chlorine isotopes in order to make an isotopic assignment of a radiochlorine isotope. Isotope separation experiments performed after bombardment should also prove useful for isotopic identification. However, for the use of a radioactive substance in a chemical or biological problem a knowledge of the atomic number is sufficient, and radioactive isotopes whose mass numbers have not been established can be used.

When a radioactive isotope is formed as the result of a reaction which involves a rare isotope, the bombardment of the separated isotope will, of course, result in a larger yield. That this may be a matter of practical importance is strikingly shown in the case of the long-lived radiocarbon of Ruben and Kamen, which is produced by the deuteron-activation of carbon. Its long half-life and the fact that it is made from C^{13}, an isotope of 1 per cent abundance, leads, under the present methods of production, to rather low intensities. However, the bombardment of nearly pure C^{13}, now available in good quantity as a result of the experiments of Urey and coworkers, makes it possible to increase the yield by a factor which may become nearly as large as 100.

The type reactions leading to the formation of the artificial radioelements will now be described (these reactions also often lead to the production of stable isotopes). For brevity it will be convenient to use a simplified notation, rather than to write out the entire reaction each time. For example, the bombardment of iron with neutrons to produce radiomanganese will be described by Fe^{56} (n,p) Mn^{56}, rather than by the more cumbersome equation

$$_{26}Fe^{56} + {}_{0}n^{1} \rightarrow {}_{25}Mn^{56} + {}_{1}H^{1}$$

(where the superscripts denote mass numbers and the subscripts atomic numbers). The notation n = neutron, p = proton, α = alpha-particle, d = deuteron, and γ = gamma-ray will be used.

The discussion which follows will also include a few statements regarding the yield of radioelements formed in the various reactions. It must be emphasized that only rough qualitative statements can be made, since the situation is too complex to allow a quantitative treatment in a few words. No summary of experimental data on the various reaction yields and the variation of the yields with energy and atomic number has been published; a summary of this type awaits more systematic data. Weisskopf and Ewing (W25) have recently published an excellent theoretical treatment of the yields from neutron, proton, and alpha-particle reactions.

It may be helpful to point out that the considerations of Bohr (B32, B33) have led to the view that the transmutation which occurs as the result of the impact of any particle with an atomic nucleus (with a few exceptions) proceeds by a mechanism which must be treated as two independent processes: namely, (*1*) the amalgamation of the particle with the nucleus to form an intermediate metastable compound nucleus, and (*2*) the eventual breaking up of the intermediate nucleus into the end products.

1. Neutron reactions

Neutrons are obtained from two types of sources,—(*1*) artificial and (*2*) those which utilize the radiations from the natural radioelements. The neutrons from the latter type are usually produced by the reaction Be^{9} (α,n) C^{12} and the sources may be prepared by mixing powdered beryllium with alpha-particle emitters such as radium, radon, or polonium. Neutrons produced in this manner have a more or less continuous distribution in energy extending up to about 13 Mev. (million electron volts[10]) for radon alpha-particles (D21, B39). The action of mono-energetic gamma-rays (of sufficient energy) on beryllium and on deuterium gives rise to mono-energetic neutrons, usually known as "photo-neutrons," with energies of the order of hundreds of kilovolts when gamma-rays from the natural radioelements are used.

Artificial sources of neutrons are obtained by bombarding various ele-

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[10] The electron volt, a unit of energy widely used in atomic and nuclear physics, is equal to 1.59×10^{-12} ergs (the amount of energy acquired by a particle of electronic charge when it falls through a potential difference of 1 volt).

ments with fast-moving charged particles, the energy of the neutrons depending upon the energy of the bombarding particles. However, the neutron energies have a very strong dependence upon the reactions used for their production, so that, taking into account the experimental conditions being used at present for their production, certain very rough statements can be made with regard to the energies of neutrons from various artificial sources. Two common sources are (*1*) deuterons (say 5 to 10 Mev.) on beryllium (the Be + D source), giving neutrons with energies extending up to about 13 Mev., and (*2*) deuterons on deuterium (the D−D source). The D−D source is used to most advantage when deuterons with energy of the order of a few hundred kilovolts are available, and under these conditions gives rise to neutrons within the narrow energy range of 2.5 to 3 Mev. The bombardment of lithium or boron with deuterons produces neutrons with energies extending up to about 20 Mev. Neutrons in this high energy range are produced also by the bombardment of beryllium with very high energy (e.g., 16 Mev.) deuterons.

Common usage has evolved a *rough* classification of neutrons into groups on the basis of their energy. "Very fast" neutrons, often called "fast" neutrons, are those, e.g., from a lithium plus deuterons (Li + D) or boron plus deuterons (B + D) source, with energies extending from about 20 Mev. to about 10 Mev., while neutrons with energies within the range starting at about 10 Mev. and extending down to an indefinite energy region (of the order of thousands of electron volts) are known as "fast" neutrons or "medium fast" neutrons (especially those at the lower end of this energy range). "Slow" or "thermal" neutrons is the name given to those neutrons which have suffered a sufficient number of collisions, usually with hydrogen nuclei as the result of passage through paraffin or water, to slow them to thermal velocities, that is, about 0.025 electron volt of energy. Slow neutrons were discovered by Fermi and coworkers (A1), and these authors give a discussion of their properties and of the slowing process. Neutrons in the energy range immediately above the thermal range are sometimes designated as "resonance" neutrons, a result of the fact that many nuclei absorb such neutrons only within extremely narrow energy ranges, that is, absorb them in a resonance fashion.

Reactions between neutrons and nuclei produce artificial radioelements by four main types of transmutations: (*1*) the simple, radiative capture, known as the n,γ reaction; (*2*) neutron capture followed by proton emission, or the n,p reaction; (*3*) neutron capture with alpha-particle emission, the n,α reaction; and (*4*) neutron capture followed by the emission of two neutrons (net expulsion of one neutron), or the $n,2n$ reaction. The n,γ and $n,2n$ reactions give radioelements which are isotopic with the target element, and hence the Szilard–Chalmers method of concentration is used when it is desired to obtain a high ratio of activity to inactive material, that is, a high *specific activity*. When the *n,p* or *n,α* reactions are used or the Szilard–Chalmers method employed, large amounts of material can be used effectively in order to obtain large specific activities. Radioelements formed in the *n,2n* reaction are largely positron emitters, while the other reactions usually lead to negative beta-particle emitters.

The *n,γ* type of activation occurs largely with slow neutrons and only to a smaller extent with fast neutrons. Elements throughout the entire range of the Periodic Table can be activated in this manner; the cross sections for slow neutron absorption, which are extremely large for some elements, vary in an irregular manner from element to element and from isotope to isotope. The *n,p* and *n,α* transmutations require fast neutrons (except for two or three cases in the lightest elements). The energy required increases regularly as one proceeds up the Periodic Table, since the outgoing charged particles must escape the nuclear potential barrier, and for atomic numbers as high as 50 only the "very fast" neutrons are effective. The *n,2n* reaction requires "very fast" neutrons because the net result is the expulsion of a neutron, whose binding energy amounts to about 8 Mev. for most of the elements.

There is another type of activation by fast neutrons which involves those isomers in which the ground state is stable. The kinetic energy of the captured neutron excites the nucleus to its upper, radioactive, isomeric state, a neutron being reëmitted, with reduced energy, after the excitation process. In keeping with our method of writing nuclear reactions, this method of excitation is known as an *n,n* process and a typical example is written In^{115} (*n,n*) In^{115*}. (The asterisk, as used here, denotes a radioactive isomer of a stable nucleus.)

2. Deuteron reactions

The most intense radioactivities are, in general, induced as the result of bombardments with high-energy deuterons which are produced in the "cyclotron" of Lawrence and Livingston (L37, L33). Most of the cyclotrons which are now in operation are producing deuterons of 5- to 10-Mev. energy and currents of 10 to 200 microamperes; the 60-in. cyclotron at Berkeley is furnishing 16-Mev. deuterons at 100 to 200 microamperes (L38). Other types of artificial sources induce radioactivities of lower intensities, since they produce deuteron beams of much lower energy.

Artificial radioelements, both negative and positive beta-particle emitters, are produced by deuterons in the following ways: (*1*) deuteron capture and proton emission, known as the *d,p* reaction, which is, since the net result is the capture of a neutron, equivalent to the *n,γ* reaction; (*2*) deuteron capture followed by neutron emission, or *d,n* reaction; and (*3*) deuteron capture with alpha-particle emission, the *d,α* reaction. The yields from all of these reactions increase with increasing energy of the deuterons and, for a given deuteron energy, decrease with increasing atomic number of the target element. This decrease is most marked for the *d,α* reaction, since the outgoing, doubly charged alpha-particles must penetrate the Coulomb barrier of the nucleus (for example, with 8-Mev. deuterons this reaction is not observed for nuclei of atomic number as high as 50, while the *d,p* and *d,n* reactions are observed throughout the entire range of the Periodic Table). It should be pointed out that the *d,p* reaction occurs largely by a mechanism known as the Oppenheimer–Phillips process (O7, V9), wherein the deuteron, upon approaching the nucleus, is polarized in such a manner as to give rise to the capture of the neutron without the usual amalgamation of the bombarding particle (deuteron) to form a temporary intermediate nucleus.

Radioelements are also produced by the *d,2n* transmutation, especially when the deuterons have an energy as high as 16 Mev. The *d,γ* and *d,d* reactions have not yet been established.

A few examples will serve to illustrate the intense radioactivities which are induced with deuterons. The bombardment of copper for 20 min. with 20 microamperes of 8-Mev. deuterons produces Cu^{64} (half-life 12.8 hr.), by the reaction Cu^{63} (*d,p*) Cu^{64}, with an intensity of about 5 millicuries, (i.e., 5×10^{-3} curies). Such a sample would give a discharge rate corresponding to about 10^7 times the natural background of an ordinary, Lauritsen, quartz-fiber electroscope. In a typical experiment a 4-hr. bombardment of phosphorus with 100 microamperes of 16-Mev. deuterons produced about 50 millicuries of P^{32} (half-life 14.3 days or 1.24×10^6 sec.) by the reaction P^{31} (*d,p*) P^{32}. With the aid of the relation $-dN/dt = \lambda N$, where $-dN/dt$ is the number of disintegrations per second and λ the disintegration constant[11], we find for N, the number of active atoms, $3.7 \times 10^{10} \times 0.05 \times 1.24 \times 10^6/0.69 = 1/3 \times 10^{16}$. This corresponds to approximately one-sixth of a microgram of radioactive P^{32}. It seems certain that it will soon be possible to produce weighable amounts of the very long-lived transmutation products.

3. *Alpha-particle (helium ion) reactions*

Helium ions which are accelerated by electrical means are entirely equivalent to alpha-particles from the natural radioelements and therefore are often called alpha-particles. However, artificially accelerated helium ions, because of the larger intensity of particles available, have largely displaced the natural alpha-particles for the production of radioelements.

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[11] The disintegration constant, λ, defined by the equation $-dN/dT = \lambda N$, is equal to 0.69 divided by the half-life.

For example, 100 mg. of radium (with its decay products) emits about 10^{10} alpha-particles per second, spread out in all directions, while 1 microampere of alpha-particles corresponds to 10^{13} particles per second, directed upon the target. When the cyclotron is in adjustment for deuterons it is also almost in adjustment for alpha-particles, since deuterons and helium ions have nearly the same value of e/m, and because the alpha-particles have the same velocity and twice the mass they attain twice the energy that deuterons do when they are accelerated with the same voltage. Most of the cyclotrons now in operation furnish alpha-particles of 10- to 16-Mev. energy. The 60-in. Berkeley cyclotron is producing 32-Mev. alpha-particles at currents of 10 to 20 microamperes.

Artificial radioelements, both negative and positive beta-particle emitters, are produced as the result of alpha-particle capture followed by neutron emission, the α,n reaction, and by alpha-particle capture and proton emission, the α,p reaction. The yields increase with increasing energy of the projectile and, for a given energy, decrease with increasing atomic number. The α,n reaction occurs with elements throughout almost the entire Periodic Table when 16-Mev. alpha-particles are used, while the α,p reaction is a very rare occurrence for elements of atomic number as high as 50.

The α,γ reaction has not yet been observed, although it might be expected to occur at an energy below that of the α,n threshold. The $\alpha,2n$ reaction has been shown to occur with 32-Mev. alpha-particles, and the calculations of Weisskopf and Ewing (W25) predict that this reaction should be important for particles of such high energy. The α,pn (or α,d) reaction has also been observed at high energies.

The excitation of nuclei by a process which might be designated as an α,α reaction is another method of activation which occurs with alpha-particles. Theoretical considerations of Weisskopf (W26) suggest, however, that this activation occurs as a result of an interaction between the electric fields of the alpha-particle and the nucleus and not as a capture and reëmission of the bombarding particle as in the case of the n,n reaction.

4. Proton reactions

Just as in the case of deuterons and alpha-particles, the cyclotron offers the best source of high-energy protons. Many investigators, especially DuBridge and coworkers, have prepared a large number of radioelements by means of proton bombardments.

The most common reaction is the capture of the proton followed by neutron emission, or the p,n reaction, producing mainly elements which decay by positron emission (or K-electron capture). The yield increases with the energy of the proton and decreases with the atomic number of the target element. This transmutation is observed throughout the entire range of the Periodic Table when 6.5-Mev. protons are used. If the radioactive substance formed in a *p,n* reaction emits positrons and thus returns to the target element, the energy threshold for the reaction is equal to the difference between the neutron and hydrogen mass (0.8 Mev.) plus the mass of two electrons (1.0 Mev.) plus the upper energy limit of the positron spectrum from the radioactive substance. (Similarly the energy threshold for the formation of a positron emitter from a *d,2n* reaction is equal to 4.0 Mev. plus the positron upper energy limit.) When the radioactive product decays by *K*-electron capture, the energy threshold may be as much as 1 Mev. lower than that which would be calculated for the formation of an emitter of zero-energy positrons.

The radiative capture of the proton, known as the p,γ reaction, is observed with the very lightest elements, and it has also been observed with a few elements of medium weight ($Z = 30$). This reaction is important only at energies below or near the threshold for the *p,n* reaction. The yield from this reaction, especially for the very lightest elements, exhibits sharp maxima at certain sharply defined energies of the protons corresponding to definite "resonance levels."

The p,α reaction has been reported only rarely but will certainly be a common occurrence when protons of higher energy become the object of experimentation. Similarly, the *p,2n* reaction is to be anticipated at high energies. The utilization of the kinetic energy of protons to excite nuclei by the *p,p* reaction occurs, as in the case of the *n,n* and the α,α reactions.

5. Gamma-ray reactions

Gamma-rays of very high energy are capable of ejecting neutrons from atomic nuclei to produce radioelements by the γ,n reaction, a type of transmutation also known as "photo-disintegration." Bothe and Gentner (B20), who have studied this reaction using the 17-Mev. gamma-rays produced in the reaction of protons with lithium and the 12-Mev. gamma-rays from boron plus protons, found that the yield varied irregularly from element to element. Mainly positron emitters are formed and the yield is comparatively low. The reactions giving rise to gamma-rays of very high energy are of the resonance type, occurring at voltages below 1 Mev., and hence the direct acceleration type of apparatus, operating at high beam currents, is the best source.

High-energy x-rays have been used to excite certain stable nuclei to their isomeric, radioactive states. This type of excitation has also been effected by bombardment with high-energy electrons (C39).

6. *Uranium and thorium fission*

In January, 1939, Hahn and Strassmann (H14) reported their very important discovery that the bombardment of uranium with slow or fast neutrons resulted in its cleavage into pairs of radioactive products of medium atomic weight. The existence of this entirely new type of nuclear reaction was immediately confirmed in many laboratories throughout the world, and Meitner and Frisch (M23), after confirming the reaction, suggested the name "fission" for the process. Subsequent work by a large number of investigators has resulted in the chemical identification of many of the fission products. Hahn and Strassmann (H15) and others found that thorium also undergoes nuclear fission when bombarded with fast neutrons, and v. Grosse, Booth, and Dunning (G7) found that the same is true for protoactinium (slow neutrons are ineffective in these cases). The products of these cleavage processes, because of the high neutron to proton ratio in uranium and thorium, have an abnormally high neutron to proton ratio; hence all are negative beta-particle emitters and many chains of successive decay are found. The radioactive isotopes formed in this manner, some of which can be formed in no other way and others of which can also be formed by some of the methods outlined in the sections above, have already found application to chemical and biological problems. Turner (T8) has published in the issue of *Reviews of Modern Physics* for January, 1940, an excellent, complete review of nuclear fission.

The events leading to the discovery of the fission process present an interesting history. In their original work Fermi and coworkers (A1) bombarded uranium with neutrons and obtained a series of radioactivities which, on the basis of chemical experiments, they were led to assign to "transuranic elements," that is, elements with atomic number greater than 92. The experiments of Hahn, Meitner, and Strassmann (H37) and others appeared to confirm this point of view, and for several years the transuranic elements were the subject of much experimental work and discussion, including a review of their chemical properties which was published in *Chemical Reviews* (Q1) in 1938. Curie and Savitch (C33), in 1938, found a product of 3.5 hr. half-life which had the chemical properties of a rare earth, but they failed to give a complete interpretation of this astonishing discovery. Early in 1939 Hahn and Strassmann (H14) described experiments which made it certain that they had observed the production of radioactive barium isotopes as the result of the bombardment of uranium with neutrons. Subsequent work has shown that practically all of the radioactivities formerly ascribed to transuranic elements are actually due to fission products. More than fifty radioactive fission products are now known and are included in table 2. The fission of uranium and thorium by deuterons (K26) and by high-energy gamma-rays (H59) has also been observed.

It has been shown by von Halban, Joliot, and Kowarski (H38), and confirmed by many others, that secondary neutrons are emitted during the fission of uranium. The secondary neutrons might themselves produce still more fissions and the possibility of the occurrence of a catastrophic chain reaction, under the proper conditions, has been the subject of much discussion and speculation. The large energy per fission (~ 200 Mev.) shows that the propagation of such a chain might involve the release of terrific amounts of energy in a very short time.

VI. TABLE OF ARTIFICIAL RADIOELEMENTS

Table 2 presents a complete list of all the artificial radioelements known to date (covering publications received prior to August 1, 1940), together with a number of important features associated with them. The natural radioactivities are not included. The plan of presentation is the same as that used by Livingood and Seaborg (L35).

The first and second columns give the atomic numbers and the mass numbers associated with the radioactivities. The degree of certainty of each assignment is indicated, in the column headed "class," with a letter according to the following code:

A = isotope certain (mass number and element certain),
B = isotope probable, element certain,
C = one of few isotopes, element certain,
D = element certain,
E = element probable,
F = insufficient evidence,
G = probably in error (e.g., impurity or inadequate half-life determination).

The fourth column lists the type of radiation, with the following meaning for the symbols:

β^- = negative beta-particles,
β^+ = positive beta-particles (positrons),
γ = gamma-rays,
e^- = internal-conversion electrons,
K = K-electron capture,
$I.T.$ = isomeric transition (transition from upper to lower isomeric state).

In the few cases where it is certain that no gamma-rays are emitted, this fact is expressed explicitly by the symbol "No γ." Annihilation gamma-rays[12] are not listed.

The half-life, followed by the relevant reference, is given in the fifth column. For the case where more than one value for the half-life has been reported, an attempt has been made to list the best value (an experimental value near the mean or one determined with a strong sample).

In the column headed "energy of radiation," the energy value is followed by the corresponding reference and by a description of the method used for the energy determination. The beta-particle energies correspond to the observed upper limits of the spectra; in those cases where only the Konopinski–Uhlenbeck (K14) extrapolated value has been reported, this is listed, followed by the designation "K.U." The methods used for the determination of the energy of the particles are described in each case with the aid of the following symbols: abs. = absorption, cl. ch. = cloud chamber with magnetic field, spect. = electron magnetic spectrograph or spectrometer.

The symbols used to describe the methods employed for the determination of the gamma-ray energies have the following meaning: abs. = absorption, cl. ch. recoil = secondary electrons in cloud chamber with magnetic field, cl. ch. pair = positron–electron pairs in cloud chamber with magnetic field, coincid. abs. = secondary electrons with coincidence counters and absorber, spect. conv. = internal-conversion electrons with magnetic spectrograph, spect. = secondary electrons with magnetic spectrograph, and abs. of e^- = absorption of internal-conversion electrons. When internal-conversion electrons are emitted the energy listed is always that of the corresponding gamma-ray transition.

The observed nuclear reactions (giving the target element, projectile, and residue, in order) by which the radioactive isotopes are formed, and the corresponding references, are listed in the last column (p = proton, n = neutron, α = alpha-particle, d = deuteron, γ = gamma-ray). The neutron-induced fission reactions of the heavy elements are included and are designated by such symbols as U-n, Th-n, and Pa-n. In those cases where the radioactive fission product is known to be the second (or later) element in a chain decay its production is not designated by these symbols (U-n, etc.) but is listed as produced by the beta-decay of its immediate parent isotope.

No attempt has been made to list all of the publications connected with a given radioactivity, since it has been the aim to keep the table as compact

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[12] Positron emission is always accompanied by "annihilation" gamma-radiation. Each positron, together with an electron (of equal mass), eventually undergoes annihilation with the emission of two gamma-rays, each with an energy (0.51 Mev.) corresponding to mc^2, where m is the electronic mass.

TABLE 2

Complete list of induced radioactivities

(The literature has been covered up to July 15, 1940)

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
1	H^3	A	β^-	>10 yr. (A16)	~0.013 (A7, O6) abs.		D-*d*-*p* (A7, A16) Be-*d*-H^3 (O6, A16)
2	He^6	A	β^-	0.8 sec. (B1)	3.7 (B1, B2) cl. ch.		Be-*n*-α (B1, P1, B3) (Li-*n*-*p*) (K1)
3	Li^8	A	β^-, α	0.88 sec. (L1)	12(β^-) (B4) cl. ch.		Li-*d*-*p* (C1, L1, R14, D1) B-*n*-α (L24) (Li-*n*-γ) (K1)
4	Be^7	A	*K*, γ	53 days (H30)		0.45 (R1, M1) abs. Pb	Li-*d*-*n* (R1, R13) B-*p*-α (R1, M1) Li-*p*-*n* (H30, H2)
	Be^{10}	A	β^-, γ	>>10^3 yr. (M22)	~0.5 (M22) abs.	<0.5 (M22) abs.	Be-*d*-*p* (M22)
5	B^{12}	A	β^-	0.022 sec. (C2, B22)	12 (B4) cl. ch.		B-*d*-*p* (C2, F1, B5)
6	C^{10}	A		8.8 sec. (B27)	3.4 (D26) cl. ch.		B-*p*-*n* (B27, D26)
	C^{11}	A	β^+	21.0 min. (R11)	0.95 (D26) cl. ch.		B-*d*-*n* (F1, C4, Y1) B-*p*-γ (C3, B23) B-*p*-*n* (B23) N-*p*-α (B23) C-*n*-2*n* (P2)
	C^{14}	A	β^-	>>10^3 yr. (K24)	0.090 (R17) abs.		C-*d*-*p* (R17) N-*n*-*p* (R11)
7	N^{13}	A	β^+, γ	9.93 min. (W14)	0.92, 1.20 (L22) spect.	0.28 (R2) cl. ch. recoil	C-*d*-*n* (H3, Y1, C4, F1) C-*p*-γ (H3, C4) B-α-*n* (E1, R3) N-*n*-2*n* (P2)
	N^{16}	A	β^-	8 sec. (C5, N1)	6.0(?) (F1) cl. ch.		N-*d*-*p* (F1) O-*n*-*p* (C5) F-*n*-α (N1, P1, N4)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
8	O^{15}	A	β^+	126 sec. (M3, B20)	1.7 (F1) cl. ch.		N-*d*-*n* (M3, F1) O-γ-*n* (B20) O-*n*-2*n* (P2) N-*p*-γ (D2) C-α-n (K3)
	O^{19}	A	β^-	31 sec. (N1)			F-*n*-*p* (N1, A1)
9	F^{17}	A	β^+	70 sec. (N2)	2.1 (K4) cl. ch.		O-*d*-*n* (N2, F1) N-α-*n* (R3) O-*p*-γ (D2)
	F^{18}	A	β^+	112 min. (S1)	0.7 (Y2) cl. ch.		Ne-*d*-α (S1) O-*p*-*n* (D2) F-*n*-2*n* (P2) O-*d*-*n* (D22, Y2)
	F^{20}	A	β^-, γ (B50, C47)	12 sec. (C1)	5.0 (F1, B50) cl. ch.	2.2 (B50) cl. ch. recoil	F-*d*-*p* (F1, C1) F-*n*-γ (N1) Na-*n*-α (N1)
10	Ne^{19}	A	β^+	20.3 sec. (W7)	2.20 (W7) cl. ch.		F-*p*-*n* (W7)
	Ne^{23}	A	β^-	40 sec. (A1, B6)	4.1 (P21) abs.		Na-*n*-*p* (A1, N1, P1) Mg-*n*-α (A1, B6) Ne-*d*-*p* (P21, W24)
11	Na^{21}	B		23 sec. (C27)			Ne-*p*-*n* (C27) Ne-*d*-*n* (P21)
	Na^{22}	A	β^+	3.0 yr. (L3)	0.58 (L3) cl. ch.	1.3 (O2) spect.	Mg-*d*-α (L3) F-α-*n* (L3, M4) Ne-*d*-*n* (L3)
	Na^{24}	A	β^-, γ	14.8 hr. (V1)	1.4 (L21) spect.	1.46, 2.0, 3.03 (C28) spect.	Na-*d*-*p* (L4, V1) Na-*n*-γ (A1) Mg-*n*-*p* (A1) Al-*n*-α (A1) Mg-*d*-α (H4)
12	Mg^{23}	A	β^+	11.6 sec. (W7)	2.82 (W7) cl. ch.		Na-*p*-*n* (W7, D9)
	Mg^{27}	A	β^-, γ	10.2 min. (H4)	1.8 (C13) cl. ch.	0.9 (R4) cl. ch. recoil	Mg-*d*-*p* (H4) Mg-*n*-γ (A1) Al-*n*-*p* (A1)
13	Al^{26}	A	β^+	7.0 sec. (W7, F2)	2.99 (W7) cl. ch.		Na-α-*n* (M4, F2) Mg-*p*-*n* (W7, D9) Mg-*p*-γ (C29)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
13	Al^{28}	A	β^-, γ	2.4 min. (A1, M5, E2)	3.3 (C6) cl. ch.	2.3 (C6) cl. ch. recoil	Al-*d*-*p* (M5) Al-*n*-γ (A1) Si-*n*-*p* (A1) P-*n*-α (A1) Mg-α-*p* (E2, R3)
	Al^{29}	A	β^-	6.7 min. (B25)	2.5 (B25) cl. ch. and abs.		Mg-α-*n* (B25, H21, F3)
14	Si^{27}	A	β^+	3.7–4.9 sec. (K8, C27)	3.74 (M21) cl. ch.		Al-*p*-*n* (K8, M21, C27)
	Si^{31}	A	β^-	170 min. (N3)	1.8 (K4) cl. ch.	No γ (N3)	Si-*d*-*p* (N3) Si-*n*-γ (A1) P-*n*-*p* (A1, P2) S-*n*-α (S2, C9)
15	P^{29}	A		<10 sec. (W11)			Si-*p*-*n* (W11)
	P^{30}	A	β^+	2.55 min. (R3)	3.0 (B48) cl. ch.		Al-α-*n* (R3, C7) S-*d*-α (S2) P-*n*-2*n* (P2) P-γ-*n* (B20) Si-*p*-*n* (B23) Si-*He*^{3}-*p* (A7)
	P^{32}	A	β^-	14.30 days (C8)	1.69 (L5) spect.	No γ (K4)	P-*d*-*p* (N3) P-*n*-γ (A1) S-*n*-*p* (A1) Cl-*n*-α (A1) S-*d*-α (S2) Si-α-*p* (F3)
16	S^{31}			<10 sec. (V4)			P-*p*-*n* (V4)
	S^{35}	A	β^-	88 days (L6, L58)	0.107 (L6) spect.		Cl-*n*-*p* (A3, L6, L58) S-*d*-*p* (C25)
17	Cl^{33}	A		2.8 sec. (H31)			S-*d*-*n* (H31)
	Cl^{34}	A	β^+	33 min. (S2, B21)	2.5 (B21) abs.		P-α-*n* (F2, R3, B21) S-*d*-*n* (S2) Cl-*n*-2*n* (P2) Cl-γ-*n* (B20) S-α-*p*,*n* or S-α-*d* (S45)
	Cl^{36}	A	β^+, *K*, β^-	>1 yr. (G8)	0.7(β^-) (G8) abs.		Cl-*n*-γ (G8) Cl-*d*-*p* (G8)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
17	Cl^{38}	A	β^-, γ	37 min. (V1)	1.1, 5.0 (W16) spect.	1.65, 2.15 (C28) spect.	Cl-*d*-*p* (K4, V1) Cl-*n*-γ (A1, K18) K-*n*-α (H5)
18	A^{39}	G	β^-	4 min. (P2)			K-*n*-*p* (P2)
	A^{41}	A	β^-, γ	110 min. (S3)	1.5 (K4) cl. ch. (K.U.)	1.37 (R8) cl. ch. recoil	A-*d*-*p* (S3) K-*n*-*p* (H5) A-*n*-γ (S3)
19	K^{38}	A	β^+, γ	7.7 min. (H5, R3)	2.3 (R3) abs.		Cl-α-*n* (H5, R3) Ca-*d*-α (H5) K-*n*-2*n* (P2)
	K^{42}	A	β^-	12.4 hr. (H5)	3.5 (K4) cl. ch.		K-*d*-*p* (H5) K-*n*-γ (H5, A1) Ca-*n*-*p* (H5) Sc-*n*-α (H5)
	$K^{43, 44}$	C	β^-	18 min. (W1, W12)			Ca-*n*-*p* (W1, W12)
20	Ca^{39}	F	β^+	4.5 min. (P2, W12)			Ca-*n*-2*n*(?) (P2, W12)
	Ca^{41}	B	*K*, γ, e^- (W12)	8.5 days (W12)		1.1 (W12) abs. Pb; abs. of e^-	Ca-*d*-*p* (W12) Ca-*n*-2*n* (W12)
	Ca^{45}	A	β^-, γ	180 days (W12)	0.2, 0.9 (W12) abs.	0.7 (W12) abs. Pb	Ca-*n*-γ (W12) Ca-*d*-*p* (W12, W5) Sc-*n*-*p* (W12)
	Ca^{49}	A	β^-, γ	2.5 hr. (W12)	2.3 (W12) abs.	0.8 (W12) abs. Pb	Ca-*d*-*p* (W12) Ca-*n*-γ (W12)
	Ca^{49}	B	β^-	30 min. (W12)			Ca-*d*-*p* (W12) Ca-*n*-γ (W12)
21	Sc^{42}	A	β^+	13.5 days (W10)	1.4 (W10) abs.		K-α-*n* (W10)
	Sc^{43}	A	β^+	4 hr. (W10)	0.4, 1.4 (W10) abs.	1.0 (W10) abs. Pb	Ca-α-*p* (F4, W10) Ca-*d*-*n* (W3) Ca-*p*-*n* (D2, D9)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
21	Sc^{44}	A	*I.T.*, e^-, γ (W10)	52 hr. (W10)		0.26 (W10, H26) spect. conv.	Sc-*n*-2*n* (B9) K-*α*-*n* (W10) Ca-*d*-*n* (W3) Ca-*p*-*n* (D2, D9) Ti-*d*-*α* (W4)
	Sc^{44}	A	β^+	4.1 hr. (W10)	1.5 (W10) abs.		Sc-*n*-2*n* (B9) K-*α*-*n* (W10) Ca-*d*-*n* (W3) Ca-*p*-*n* (D2, D9) Sc-*γ*-*n* (B20) Sc^{44} (52 hr.) *I.T.* (W10)
	Sc^{46}	A	β^-, γ; *K* (W5)	85 days (W5)	0.26, 1.5, (β^-) (W10) abs.	1.25 (W10) abs. Pb	Sc-*d*-*p* (W1, W5) Sc-*n*-*γ* (W1) Ti-*d*-*α* (W1) Ca-*α*-*p* (W10) Ti-*n*-*p* (W4)
	Sc^{47}	B	β^-, γ	63 hr. (W10)	1.1[a] (W10) abs.		Ca-*α*-*p* (W10) Ti-*n*-*p* (W10)
	Sc^{48}	A	β^-, γ (W10)	44 hr. (W10)	0.5, 1.4 (W10) abs.	0.9 (W10) abs.	Ti-*n*-*p* (W4, P2, W10) V-*n*-*α* (W4, P2, W10)
	Sc^{49}	A	β^-	57 min. (W10)	1.8 (W10) abs.	No γ (W10)	Ca-*d*-*n* (W10) Ca^{49} (2.5 hr.) β^- decay (W10) Ti-*n*-*p* (W10)
22	Ti^{51}	A	β^-, γ (W4)	2.9 min. (W4)			Ti-*d*-*p* (W4) Ti-*n*-*γ* (W4, A1)
	Ti^{51}	A	β^-, γ	72 days (W5)	0.36 (W5) abs.	1.0 (W5) coincid. abs.	Ti-*d*-*p* (W5) Ti-*n*-*γ* (W8)
23	V^{47}	B	*K*	600 days (W5)	No β^+ or e^- (W5)	No γ (W5)	Ti-*d*-*n* (W5)
	V^{48}	A	β^+; *K*, γ (W5)	16 days (W4)	1.0 (W4) cl. ch.	1.05 (R4) cl. ch. recoil	Ti-*d*-*n* (W4) Sc-*α*-*n* (W6) Cr-*d*-*α* (W4) Ti-*p*-*n* (D9)
	V^{49}	B	β^+	33 min. (W4)	1.9 (W4) abs.		Ti-*d*-*n* (W4) Ti-*α*-*p* (W4) Ti-*p*-*n* (D9)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
23	V^{50}	A	β^+	3.7 hr. (W4)			V-n-2n (W4) Ti-d-n (W4) Ti-α-p (W4)
	V^{52}	A	β^-	3.9 min. (W4)	2.05 (D24) abs.		V-n-γ (W4, P2, A1) V-d-p (W4) Cr-n-p (W4, P2) Mn-n-α (W4, P2, A1)
24	Cr^{51}	B	K, γ, e^- (W13)	26.5 days (W13)		0.5, 1 (W13) abs. Pb; abs. of e^-	Ti-α-n (W13) Cr-d-p (W13, A14) Cr-n-γ (W13) Cr-n-2n (A14)
	Cr^{55}	B		1.6–2.3 hr. (A14, D14)			Cr-n-γ (D14, A14) Cr-d-p (A14)
25	Mn^{51}	A	β^+	46 min. (L7)	2.0 (L7) abs.		Cr-d-n (L7) Cr-p-γ (D2, D4)
	Mn^{52}	A	β^+, γ	21 min. (L7)	2.2 (H6)	1.2 (H6)	Fe-d-α (D5, L7) Cr-p-n (H6)
	Mn^{52}	A	β^+, γ; K (H6)	6.5 days (L7)	0.77 (H6)	1.0 (H6)	Fe-d-α (L7) Cr-p-n (H6)
	Mn^{54}	A	K, γ (L7)	310 days (L7)		0.85 (L7) abs. Pb	Fe-d-α (L7) Cr-d-n (L7) V-α-n (L7) Cr-p-n (D9)
	Mn^{56}	A	β^-, γ	2.59 hr. (L7)	1.2, 2.9 (B10) cl. ch. (K.U.)	0.7, 1.7 (B26) cl. ch. recoil	Mn-n-γ (A1) Mn-d-p (L7) Fe-d-α (L7) Fe-n-p (A1) Co-n-α (A1) Cr-α-p (R3)
26	Fe^{53}	A	β^+	8.9 min. (R3)			Cr-α-n (R3) Fe-n-2n (L20)
	Fe^{55}	A	K, e^-	~4 yr. (V4)			Fe-d-p (L23) Mn-p-n (V4)
	Fe^{59}	A	β^-, γ	47 days (L20)	0.4, 0.9 (L20) abs.	1.0 (L20) abs. Pb	Fe-d-p (L20) Co-n-p (L20)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
27	Co^{55}	B	β^+, γ	18.2 hr. (D5)	1.50 (L21) spect.	0.16, 0.21, 0.8, 1.2 (C20) cl. ch. recoil	Fe-*d*-*n* (D5, L8) Fe-*p*-γ (L9)
	Co^{56}	B	*K*, γ, e^-; β^+(?) (L10)	270 days (L10)	0.4 (β^+) (L10)		Fe-*d*-2*n* (L9, B24, P4) Ni-*d*-α (L11) Fe-*p*-*n* (L9)
	Co^{58}	A	β^+, γ	72 days (L10)	<0.5 (L10) abs.	0.6 (L10) abs. Pb	Fe-*d*-*n* (L9, B24, P4) Mn-α-*n* (L9) Ni-*d*-α (L11) Fe-*p*-*n* (L9) Ni-*n*-*p* (V5, L10, L56)
	Co^{60}	A	β^-, γ	5.5 yr. (L10)	0.16, 1.5 (R9) abs.	1.3 (L9) abs. Pb	Co-*d*-*p* (L9, B24) Co-*n*-γ (R9, L9)
	Co^{60}	B	*I.T.*(?), e^- (L10)	11 min. (H7, L10)			Co-*n*-γ (H7, L8) Ni-*n*-*p* (H8)
28	Ni^{57}	A	β^+	36 hr. (L11)	0.67 (L11) abs.		Fe-α-*n* (L11) Ni-*n*-2*n*(?) (L11)
	Ni^{65}	A	β^-, γ	2.6 hr. (L11)	1.9 (L11) abs.	1.1 (L11) abs. Pb.	Ni-*d*-*p* (L11) Ni-*n*-γ (H8) Cu-*n*-*p* (H8) Zn-*n*-α (H8) Ni-*n*-2*n* (H8)
29	Cu$^{58,\ 60}$	C	β^+	81 sec. (D4)			Ni-*p*-*n* (D4)
	Cu$^{58,\ 60}$	C	β^+	7.9 min. (D4)			Ni-*p*-*n* (D4)
	Cu^{61}	B	β^+; *K* (A4)	3.4 hr. (T1, R3)	0.9 (R3) abs.	No γ (G2)	Ni-*d*-*n* (T1) Ni-*p*-*n* (D4) Ni-*p*-γ (D4) Ni-α-*p* (R3)
	Cu^{62}	A	β^+	10.5 min. (H8)	2.6 (C13) cl. ch.		Cu-*n*-2*n* (H8) Cu-γ-*n* (B20) Co-α-*n* (R3) Ni-*p*-*n* (S18) Ni-*p*-γ (S18) Cu-*d*-*p*,2*n*(?) (K22)
	Cu^{64}	A	β^-; β^+; *K* (A4)	12.8 hr. (V2)	0.58 (β^-), 0.66 (β^+) (T6, T11) spect.	No γ (T6)	Cu-*d*-*p* (V2) Cu-*n*-γ (H8) Cu-*n*-2*n* (H8) Ni-*p*-*n* (S18, D4) Zn-*n*-*p* (H8)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
29	Cu^{66}	A	β^-	5 min. (A1)	2.9 (S5) cl. ch. (K.U.)		Cu-n-γ (A1) Zn-n-p (H8) Ga-n-α (C5) Cu-d-p (L31)
30	Zn^{63}	A	β^+	38 min. (D4, B20)	2.3 (S18) abs., (T11) spect.		Zn-n-2n (H8, P2) Zn-γ-n (B20) Cu-p-n (S18, D4) Ni-α-n (R3) Cu-d-2n (L31)
	Zn^{65}	A	β^+; K, γ, e^-	250 days (L12)	0.4 (β^+) (D9) cl. ch.	0.45, 0.65, 1.0 (W15) cl. ch. recoil	Zn-d-p (L12) Cu-d-2n (P4) Cu-p-n (B12) Zn-n-γ (S6) Ga^{65}K decay (L10)
	Zn^{69}	A	$I.T.$, γ (K11)	13.8 hr. (L12)		0.47 (K11) abs. Pb	Zn-d-p (L12, K11, V7) Zn-n-γ (T2, L12) Ga-d-α (L12) Ga-n-p (L12)
	Zn^{69}	A	β^-	57 min. (L12)	1.0 (L12) abs.	No γ (L12)	Zn-d-p (L12, K11, V7) Zn-n-γ (T2) Ga-d-α (L12) Ga-n-p (L12) Zn^{69} (13.8 hr.) $I.T.$ (K11)
31	Ga^{64}	B	β^+	48 min. (B13)			Zn-p-n (B13)
	Ga^{65}	A	K, e^-	15 min. (A4, L10)		0.054, 0.117 (D9) spect. conv.	Zn-d-n (A4, L10) Zn-p-γ (D9)
	Ga^{66}	A	β^+	9.4 hr. (B13, R3)	3.1 (M7) abs.		Cu-α-n (M7, R3) Zn-p-n (B13)
	Ga^{67}	A	K, γ, e^-	83 hr. (A4)		0.0925 (V7, H25) spect. conv.; 0.18, 0.30 (H25) spect.	Zn-d-n (A4, G6, V7) Zn-α-p (M8) Zn-p-n (B13, V7)
	Ga^{68}	A	β^+	68 min. (R3)	1.9 (R3, M7) abs.		Cu-α-n (R3, M7) Ga-n-2n (P2) Ga-γ-n (B20) Zn-p-n (D2, B13) Zn-p-γ(?) (D2) Zn-d-n (G6, V7)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
31	Ga^{70}	A	β^-, γ	20 min. (B20, A1)	1.7 (S25) cl. ch. (K.U.)		Ga-*n*-γ (A1) Ga-*n*-2*n* (P2) Ga-γ-*n* (B20) Zn-*p*-*n* (D2, V7) Zn-α-*p* (M8)
	Ga^{72}	A	β^-, γ	14 hr. (S6, L20)	2.6 (L28) abs.	1.0 (S7) abs. Pb	Ga-*d*-*p* (L20) Ga-*n*-γ (S6)
32	Ge^{69}	E	β^+	29 min. (S6)			Ge-*n*-2*n* (S6)
	$Ge^{69, 71}$	C		6–10 days (S6, L28)			Ge-*n*-? (S6) Ga-*d*-2*n* (L28)
	Ge^{71}	B	β^+	26–37 hr. (M8, S25)	1.0 (M8) abs.		Zn-α-*n* (M8) Ge-*n*-γ (S6) Ge-*d*-*p* (S6) Ga-*d*-2*n* (L28) Ge-*n*-2*n* (S25)
	$Ge^{67, 69, 71}$	E		195 days (M8)			Zn-α-*n* (M8)
	$Ge^{75, 77}$	E	β^-	81 min. (S6)	1.1 (S25) cl. ch. (K.U.)		Ge-*n*-γ (S6) Ge-*d*-*p* (S6)
	$Ge^{75, 77}$	E	β^-	8 hr. (S6)	1.9 (S25) cl. ch. (K.U.)		Ge-*n*-γ (S6)
33	As^{71}	F	β^+, γ	50 hr. (S26)			Ge-*d*-*n* (S26)
	As^{71}	F	β^+, γ	88 min. (S26)			Ge-*d*-*n* (S26)
	As^{72}	E	β^+	26 hr. (V4)			Ge-*p*-*n* (V4)
	As^{74}	A	β^-, β^+, γ (S26)	16 days (S26)	1.3 (β^-), 0.9 (β^+) (S26) cl. ch. (K.U.)		As-*n*-2*n* (S26, C11) Ge-*d*-*n* (S26) Se-*d*-α (F8) Ge-*p*-*n* (D9)
	As^{76}	A	β^-, γ; β^+, *K*, γ(?) (S23)	26.8 hr. (W9)	1.1, 1.7, 2.7 (β^-) (S23, W9); 0.7, 2.6 (β^+) (S23) cl. ch.	3.2, 2.2, 1.5 (S23) cl. ch. pair	As-*d*-*p* (C11, T3) As-*n*-γ (C11) Br-*n*-α (C11) Ge-*p*-*n* (V4) Se-*n*-*p* (S26) Se-*d*-α (F8)
	As^{77}	D	β^-, γ (S26)	90 days (S26)	0.12 (S26) cl. ch. (K.U.)		Ge-*d*-*n* (S26)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
33	As^{78}	A	β^-, γ	65 min. (S9)	1.4 (S26) cl. ch. (K.U.)	0.27 (S26) abs. Pb	Br-*n*-α (S9, C11, S26) Se-*n*-*p* (S26)
34	Se^{75}	A	*K*, γ, e^-	48 days (D9)		0.50 (D9) spect. conv.	As-*p*-*n* (D9)
	$Se^{79,81}$	C	*I.T.*, e^- (L30)	57 min. (S9, L30)		0.098 (L30) spect. conv.	Se-*d*-*p* (S9, L30) Se-*n*-γ (S9, H10) Br-*n*-*p* (S9, L30) Se-γ-*n* (B20)
	$Se^{79,81}$	C	β^-	19 min. (L30)	1.5 (L30) abs.		Se-*d*-*p* (S9, L30) Se-*n*-γ (S9, H10) Se-γ-*n* (B20) Br-*n*-*p* (L30) $Se^{79,81}$ (57 min.) *I.T.* (L30)
	Se^{83}	A	β^-	30 min. (L30)			Se-*d*-*p* (L30) Se-*n*-γ (L30)
	Se	D		Several hours (B15)			Th-*n* (B15)
	Se	D		Several days (B15)			Th-*n* (B15)
35	Br^{78}	A	β^+, e^-, γ	6.4 min. (S9)	2.3 (β^+) (S9) abs.	0.046, 0.108 (V7) spect. conv.	Se-*d*-*n* (S9) As-α-*n* (S9) Br-γ-*n* (B20, C5) Br-*n*-2*n* (H10) Se-*p*-*n* (B13, V7)
	Br^{80}	A	*I.T.*, e^-, γ (S10, V3, V7, G22)	4.4 hr. (B13)		0.049; 0.037 or 0.025 (V7) spect. conv. 0.037 (G22) abs. Al	Br-*n*-γ (S9, S10, A2) Br-*d*-*p* (S9) Se-*p*-*n* (B13, V7) Br-γ-*n* (B20) Br-*n*-2*n* (P2)
	Br^{80}	A	β^-, γ	18 min. (S9, S10)	2.0 (A2) spect.	<0.5 (B13, S9) abs.	Br-*n*-γ (S9) Br-*d*-*p* (S9) Se-*p*-*n* (B13) Br-γ-*n* (B20) Br-*n*-2*n* (P2) Br^{80} (4.4 hr.) *I.T.* (S10)
	Br^{82}	A	β^-, γ	34 hr. (S9)	0.7 (B13)	0.65 (K5) cl. ch. recoil and abs.	Br-*n*-γ (K5, S9) Br-*d*-*p* (S9) Se-*p*-*n* (B13) Se-*d*-2*n* (S9) Rb-*n* α (S9, P2)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
35	Br^{83}	A	β^-	140 min. (L30)	1.05 (L30) abs.	No γ (S9)	Se-*d*-*n* (S9) Se^{83} β^- decay (S9, L30) Th-*n* (B15, L30) U-*n* (L30)
	$\mathrm{Br}^{\geq 82}$	D		40 min. (D6)			U-*n* (D6, H22, H57)
	$\mathrm{Br}^{\geq 82}$	F		22 hr. (B15)			Th-*n* (B15)
	$\mathrm{Br}^{> 82}$	D		3.8 hr. (H22)			U-*n* (H22)
36	$\mathrm{Kr}^{79,\,81}$	C	β^+ (B41)	34 hr. (B41)	0.5 (B41) cl. ch.		Kr-*d*-*p* (C45, S9) Br-*p*-*n* (B41, C41) Se-α-*n* (C45)
	$\mathrm{Kr}^{79,\,81}$	C	*I.T.*(?), e^-, γ; no β^+ (C41)	13 sec. (C41)		0.187 (C41) spect. conv.	Br-*p*-*n* (B41, C41)
	$\mathrm{Kr}^{79,\,81}$	C	*I.T.*(?), e^-, γ; no β^+ (C41)	55 sec. (C41)		0.127 (C41) spect. conv.	Br-*p*-*n* (B41, C41) Se-α-*n*(?) (K3)
	Kr^{83*}	A	*I.T.*, e^- (L30)	113 min. (L30)		0.049 (L30) abs. of e^-	Br^{83} β^-decay (L30) Se-α-*n* (C45) Kr-*d*-*p* (C45)
	Kr^{87}	E	β^-	74 min. (S9)			Kr-*d*-*p* (S9) Se-α-*n*(?) (K3)
	Kr^{87}	B	β^-	4.5 hr. (S9)			Kr-*d*-*p* (S9, C45)
	Kr^{89}	B	β^-	~2 min. (G9, G21)			U-*n* (G9, G21)
	Kr^{88}	A	β^-	3 hr. (L27, H28)			Th-*n* (H29, A5, L27) U-*n* (H28, H11, G9, G21)
	$\mathrm{Kr}^{>90}$	D	β^-	<0.5 min. (H28)			U-*n* (H28) Th-*n* (H29)
37	Rb^{82}	B		20 min. (H51)			Br-α-*n* (H51)
	Rb^{84}	B		6.5 hr. (H51)			Br-α-*n* (H51) Kr-*d*-*n* (H51)
	Rb	F		42 min. (H51)			Kr-*d*-*n* (H51)
	Rb	F		200 hr. (H51)			Kr-*d*-*n* (H51)
	Rb^{88}	A	β^-	18 min. (S9)	4.6 (G21) abs.		Rb-*n*-γ (S9, P2) Pa-*n* (G7) Kr^{88} β^-decay (H28, L27, H11, G21)
	Rb^{89}	B	β^-, γ (G21)	15 min. (G9, G21)	3.8 (G21) abs.		Kr^{89} β^-decay (G9, G21)

* Radioactive isomer of stable nucleus.

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
37	Rb$^{86,\,88}$	C	β^-	18 days (S9)			Rb-*n*-γ (S9)
	Rb$^{>90}$	D	β^-	80 sec. (H28)			Kr$^{>90}$ β^- decay (H28)
38	Sr^{85}	A	*K*, γ (D13)	65 days (D13)		0.8 (D13, D25) abs. Pb	Rb-*p*-*n* (D13, D25)
	Sr^{85}	A	*I.T.*, e^-, γ (D25)	70 min. (D25)		0.170 (D25) spect. conv.	Rb-*p*-*n* (D13, D25)
	Sr^{87}[*]	A	*I.T.*, e^-, γ (D11)	2.7 hr. (D11)		0.37 (D11) spect. conv.	Sr-*n*-*n* (D13, R15, D25) Rb-*p*-*n* (D11) Sr-*d*-*p* (D11) Sr-*n*-γ (D11, R15) Y^{87} (80 hr.) *K* decay (D11, D25) Sr-*p*-*p*(?) (D25) Zr-*n*-α (S46)
	Sr^{89}	A	β^-	55 days (S24)	1.50 (S24) cl. ch.	No γ (S24)	Sr-*d*-*p* (S11, S24) Sr-*n*-γ (S11, S24) Y-*n*-*p* (S12) Rb^{89} β^-decay (G9, H28, G21) Zr-*n*-α(?) (S46)
	Sr$^{>90}$	D	β^-	7 min. (L26)			U-*n* (L26, H28)
	Sr$^{\geq 90}$	D	β^-	6 hr. (H28, L26)			Rb$^{\geq 90}$ β^- decay (H28)
39	Y^{86}	B	*K*, γ (D25)	105 days (D25)		2 (?) (D13, (D25) abs.	Sr-*p*-*n* (D13, D25)
	Y^{87}	B	*I.T.*, e^-, γ (D25)	14 hr. (S24, D13)		0.5 (D25) abs.	Sr-*d*-*n* (S24, D13, D25) Sr-*p*-*n* (D13, D25)
	Y^{87}	A	*K* (D13)	80 hr. (D25)		No γ (?) (D25)	Sr-*p*-*n* (D13, D25) Sr-*d*-*n* (D13, S24, D25)
	Y^{88}	A	β^+	2.0 hr. (S24)	1.2 (S11) cl. ch. (K.U.)		Sr-*d*-*n* (S11, S24) Y-*n*-2*n* (S11) Sr-*p*-*n* (D13, D25)
	Y^{90}	A	β^-	60 hr. (S11)	2.6 (S11) cl. ch. (K.U.)		Y-*d*-*p* (S11) Y-*n*-γ (S11, S12) Cb-*n*-α (S42, S13) Zr-*n*-*p* (S46) Zr-*d*-α (S46)
	Y$^{>90}$	D		3.3 hr. (H28)			Sr$^{>90}$ (6 hr.) β^- decay (H28, L26) Zr-*n*-*p*(?) (S46)

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[*] Radioactive isomer of stable nucleus.

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
40	Zr^{89}	A	β^+ (S12, D13)	78 hr. (D25)	1.0 (β^+) (S12) cl. ch. (K.U.); (D25) abs.	No γ (D25)	Zr-*n*-2*n* (S12, S46) Y-*p*-*n* (D13, D25) Mo-*n*-α (S46)
	Zr^{89}	A	e^-, γ; *I.T.* or *K* (D13, D25)	4.5 min. (D25)			Y-*p*-*n* (D13, D25)
	Zr	E	β^-	18 min. (S46)			Zr-*n*-γ (S46)
	Zr	F	β^-	90 min. (S12)	~1.5 (S46) abs.		Zr-*d*-? (S12, S46)
	Zr	E	β^-	70 hr. (S46)	1.17 (S46) cl. ch. (K.U.)		Zr-*n*-? (S46)
	Zr^{93}	D	β^-	63 days (S46)	~0.25 (S46) abs.		Zr-*n*-γ (S46) Zr-*d*-*p* (S46) Mo-*n*-α(?) (S46)
	Zr^{95}	D	β^-	17.0 hr. (G18)	1 (G18) abs.		U-*n* (G18) Zr-*n*-γ (S46) Mo-*n*-α (S46)
	Zr^{97}	E	β^-	6 min. (S46)	~1.9 (S46) abs.		Zr-*n*-γ (S46)
	Zr	D	β^-	>20 days (G18)	~0.25 (G18) abs.		U-*n* (G18)
41	Cb	E		4 min.			Zr-*p*-*n*(?) (D9)
	Cb	E		12 min.			Zr-*p*-*n*(?) (D9)
	Cb	E		38 min.			Zr-*p*-*n*(?) (D9)
	Cb	E		21 hr.			Zr-*p*-*n*(?) (D9)
	Cb	E		96 hr.			Zr-*p*-*n*(?) (D9)
	Cb^{92}	A	β^-	11 days (S42, S13)	1.38 (S42) cl. ch. (K.U.)		Cb-*n*-2*n* (S42, S13) Mo-*n*-*p* (S46)
	Cb^{93*}	D	*I.T.*, e^-	~55 days (S46)		~0.15 (S46) abs. of e^-	Zr^{93} β^- decay (S46)
	Cb^{94}	A	β^-, γ (S42)	6.6 min. (S42)	1.4 (S42) abs.	0.4 (S42) abs. Pb	Cb-*n*-γ (S42, S13, P2)
	Cb^{95}	D	β^-	75 min. (G18)	1 (G18) abs.		Zr^{95} β^- decay (G18, S46) Mo-*n*-*p* (S46)

* Radioactive isomer of stable nucleus.

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
42	Mo^{93}	F		7 hr. (D9)			Cb-*p*-*n*(?) (D9)
	$Mo^{91,\,93}$	C	β^+	17 min. (B20, S12)	2.65 (S46) cl. ch. (K.U.)		Mo-*n*-2*n* (H10, S12, S46) Mo-γ-*n* (B20)
	Mo^{99}	B	β^-, γ	67 hr. (S14)	1.5 (S14) abs.	0.4 (S14) abs.	Mo-*d*-*p* (S14) Mo-*n*-γ (S14, S12) U-*n* (H23) Th-*n* (H24) Mo-*n*-2*n* (S46)
	Mo^{101}	B	β^-	19 min. (S40, S22)	1.8 (S40) cl. ch. (K.U.)		Mo-*n*-γ (S40, S22, S46)
43	43^{96}	B	β^+(?)	2.7 hr. (D4)			Cb-α-*n* (K3) Mo-*p*-*n* (D4) Mo-*d*-*n* (S14)
	43^{99}	B	*I.T.*, e^-, γ (S14)	6.6 hr. (S14)		0.136 (S14) spect. conv.; ~0.18 (S14) abs.	Mo^{99} β^- decay (S14)
	43^{101}	B	β^-	9 min. (S40, S22)	1.1 (S40) cl. ch. (K.U.)		Mo^{101} β^- decay (S40, S22 S46)
	43	D	*K*, e^-	90 days (C12)		0.096 (H25) spect. conv.	Mo-*d*-*n* (C12, C24)
	43	D	*K*, γ	62 days (C12)			Mo-*d*-*n* (C12, C24)
	43	D	*K*(?), e^-, γ (E5)	110 hr. (E3)	0.6 (E3)	0.05, 0.5 (E5)	Mo-*p*-*n* (E3, E5)
	43	E	β^-, γ (E3)	55 min. (E5)	2.5 (E5) abs.		Mo-*p*-*n* (E3, D4, E5)
	43	E	β^-	36.5 hr. (D4)			Mo-*p*-*n* (D4)
	43	E	β^-	18 sec. (D9)			Mo-*p*-*n* (D3, D9)
	43	D	*K*	~2 days (S14)			Mo-*d*-*n* (S14)
44	Ru^{95}	F		20 min. (D7)			Ru-*n*-2*n*(?) (D7, P2)
	Ru^{103}	B	β^-	4 hr. (D7, L13)			Ru-*n*-γ (D7) Ru-*n*-2*n* (D7, P2) Ru-*d*-*p* (L13)
	Ru^{105}	B	β^-	20 hr. (D7)			Ru-*n*-γ (D7)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	A				Particles	γ-Rays	
44	Ru	F	β^-	39 hr. (L13)			Ru-*d*-? (L13)
	Ru	G		11 days (L13)			Ru-*d*-? (L13)
	Ru	E		90 min. (K3)			Mo-α-*n* (K3)
45	Rh^{104}	A	*I.T.*, e^- (P5)	4.2 min. (P5)		0.055–0.080 (P5) abs. of e^-	Rh-*n*-γ (P5, A1, P2) Ru-*p*-*n* (D9)
	Rh^{104}	A	β^-	44 sec. (P5, A1)	2.3 (C13) cl. ch.		Rh-*n*-γ (P5, A1) Rh^{104} (4.2 min.) *I.T.* (P5) Ru-*p*-*n* (D9)
	Rh^{105}	B	β^-	46 days (L13)			Ru^{105} β^- decay (D7) Ru-*d*-*n* (L13)
	Rh	G	β^-	1.1 hr. (P2)			Rh-*n*-? (P2)
	Rh	E		8 hr. (D9)			Ru-*p*-*n*(?) (D9)
	Rh	E		10.7 hr. (D9)			Ru-*p*-*n*(?) (D9)
	Rh	E		3 days (D9)			Ru-*p*-*n*(?) (D9)
46	$Pd^{107,\,109}$	C	β^-	13 hr. (K6)	1.03 (K6) cl. ch.		Pd-*d*-*p* (K6) Pd-*n*-γ (A1, K6) Ag-*n*-*p* (F5)
	Pd^{111}	A	β^-	17 min. (K6)			Pd-*d*-*p* (K6, A1) Pd-*n*-γ (K6, A1)
47	Ag^{102}	E		73 min. (E6)			Pd-*p*-*n* (E6)
	Ag^{104}	E		16.3 min. (E6)			Pd-*p*-*n* (E6)
	Ag^{105}	E	*K*	45 days (E6)		0.29, 0.42, 0.50, 0.62 (E6) spect.	Pd-*p*-*n* (E6)
	Ag^{106}	A	β^+	24.5 min. (P6, D2)	2.04 (F5) abs.	No γ (F5)	Ag-*n*-2*n* (P6) Pd-*d*-*n* (P6) Cd-*n*-*p* (P6) Rh-α-*n* (P6, K3) Ag-γ-*n* (B20) Pd-*p*-γ (D2) Pd-*p*-*n* (D2, E6)
	Ag^{106}	A	*K*(?), e^-, γ (P6, F5, A4)	8.2 days (P6, K6)	1.2 (e^-) (F5) abs.	1.06, 0.69 (E6) spect.	Ag-*n*-2*n* (P6, K6) Pd-*d*-*n* (P6, K6) Rh-α-*n* (P6) Pd-*p*-*n* (D2, E6) Cd-*n*-*p* (P6) Ag-*d*-*p*,2*n*(?) (K23)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
47	Ag$^{107*, 109*}$	C	*I.T.*, e^-	40 sec. (A12)		0.093 (V7, A12) spect. conv.	Cd$^{107, 109}$ (6.7 hr.) *K* decay (A12) Cd$^{107, 109}$ (~90 days) *K* decay (H25) Ag-*n*-*n* (A12)
	Ag^{108}	A	β^-	2.3 min. (A1, B20)	2.8 (N4) cl. ch.		Ag-*n*-γ (A1) Ag-γ-*n* (B20) Pd-*p*-*n* (D2, E6) Cd-*n*-*p* (P6) Ag-*d*-*p* (K12)
	Ag^{110}	A	β^-, γ (P6)	22 sec. (A1, P6)	2.8 (G4) cl. ch. (K.U.)		Ag-*n*-γ (A1) Cd-*n*-*p* (P6)
	Ag$^{108, 110}$	C	β^-	225 days (L14, R10)			Ag-*n*-γ (R10, L14, A8, M12) Ag-*d*-*p* (K12)
	Ag^{111}	A	β^-	7.5 days (K6, P6)		No γ (K6, P6)	Pd-*d*-*n* (K6, P6) Pd-α-*p* (P6) Cd-*n*-*p* (P6) Pd^{111} β^- decay (K6) U-*n* (N9)
	Ag^{112}	A	β^-, γ	3.2 hr. (P6)	2.2 (P6) cl. ch.		Cd-*n*-*p* (P6) In-*n*-α (P6) U-*n* (N9)
48	Cd$^{107, 109}$	C	*K*, γ (D4, V7, W11, A12)	6.7 hr. (D4, R5)		0.53 (V7) abs. Pb	Ag-*p*-*n* (D4, R5, V7, W11) Ag-*d*-2*n* (K12, A12)
	Cd$^{107, 109}$	C	*K*	~90 days (H25)			Ag-*d*-2*n* (H25)
	Cd^{109}	E	β^+	33 min. (P2)			Cd-*n*-2*n* (P2)
	Cd^{115}	A	β^-, γ	2.5 days (G5)	1.11 (C14) spect.	0.55 (L57) cl. ch. recoil	Cd-*d*-*p* (C14) Cd-*n*-γ (G5, M10) Cd-*n*-2*n* (G5) U-*n* (N9)
	Cd^{117}	A	β^-	3.75 hr. (C14)			Cd-*d*-*p* (C14) Cd-*n*-γ (M10, G5) U-*n* (N9)
	Cd*	D	*I.T.*, e^-	50 min. (D8)			Cd-*n*-*n* (D8) U-*n* (?) (N9)
49	In^{110}	D	β^+	65 min. (B17)	1.6 (B17) spect.		Cd-*p*-*n* (B17) Ag-α-*n* (K9) Cd-*d*-2*n* (L57)
	In^{110}	D	β^+, γ, e^-	20 min. (B17)	1.7 (β^+) (L57) cl. ch.	0.16 (B17) spect. conv.	Cd-*d*-2*n* (L57) Cd-*p*-*n* (B17) Ag-α-*n* (K3, K9)

* Radioactive isomer of stable nucleus.

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
49	In^{112}	D	K, γ, e^- (L57)	2.7 days (B17, C14)		0.17, 0.25 (B17, C14) spect. conv.	Cd-p-n (B17) In-n-$2n$ (C14) Cd-d-n (L57) Ag-α-n (L57)
	In^{113*}	A	$I.T., \gamma, e^-$ (B17)	105 min. (B17)		0.39 (B17, L57) spect. conv.	Cd-p-n (B17) Sn^{113} K decay (B17, S22) Cd-d-n (L57)
	In^{114}	A	$I.T., e^-$ (L57, L48)	48 days (B17)		0.19 (B17, L57) spect. conv.	In-n-γ (L15, M12) Cd-p-n (B17) In-d-p (L57) Cd-d-n (L57) In-n-$2n$ (L57)
	In^{114}	A	β^-	72 sec. (L15, B17)	1.98 (L32) cl. ch.		In^{114} (48 days) *I.T.* (L48, L57) In-n-$2n$ (L15, P2) In-γ-n (B11, C5) Cd-p-n (B17)
	In^{115*}	A	$I.T., e^-, \gamma$ (L57)	4.1 hr. (G5, B18)		0.34 (L57) spect. conv.	In-n-n (G5) In-p-p (B18) In-α-α (L16) In-x-rays (P7, C10) Cd^{115} β^- decay (G5) Cd-d-n (L57)
	In^{116}	A	β^-	13 sec. (A1, C14)	2.8 (C14) cl. ch.	No γ (M11)	In-n-γ (A1, L15) In-d-p (L15) Cd-p-n (D9)
	In^{116}	A	β^-, γ	54 min. (A1, L15)	0.85 (C14, C44) spect. and cl. ch.	1.8, 1.4, 1.0, 0.6, 0.4, 0.2 (C44) cl. ch. recoil	In-n-γ (A1, M11) Cd-p-n (B17) In-d-p (L15)
	In^{117}	A	β^-, γ, e^-	117 min. (L32)	1.73 (β^-) (C14) spect.		Cd^{117} β^- decay (G5) Cd-d-n (C14, L57)
50	Sn^{113}	A	K, e^-, γ	70–105 days (L17, B17)		0.085 (B17) spect. conv.	In-p-n (B17) Sn-d-p (L17) Cd-α-n (L17)
	Sn<^{119}	E	β^-	25 min. (L17)			Cd-α-n (L17)
	Sn<^{119}	E	β^-	3 hr. (L17)			Cd-α-n (L17)
	Sn<^{119}	E	β^-	13 days (L17)			Cd-α-n (L17)
	Sn<^{126}	D	β^-	40 min. (L17)			Sn-d-p (L17) Sn-n-γ (L17) Sn-n-$2n$ (P2)

* Radioactive isomer of stable nucleus.

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	A				Particles	γ-Rays	
50	Sn<^{126}	D	β^-	26 hr. (L17)			Sn-*d*-*p* (L17) Sn-*n*-γ (L17)
	Sn<^{126}	D	β^-	10 days (L17)			Sn-*d*-*p* (L17) Sn-*n*-γ (L17)
	Sn<^{126}	D		~400 days (L17)			Sn-*d*-*p* (L17)
	Sn^{125}	B	β^-	9 min. (L17)			Sn-*d*-*p* (L17) Sn-*n*-γ (L17)
51	Sb	E	β^-	3.5 min. (D9)			Sn-*p*-*n* (D9)
	Sb$^{116,\,118}$	E	β^+	3.6 min. (R16)			In-α-*n* (L16, R16)
	Sb^{120}	A	β^+	17 min. (H10, L18)	1.53 (A10) cl. ch.		Sb-*n*-2*n* (P2, H10) Sb-γ-*n* (B20) Sn-*d*-*n* (L18) Sn-*p*-*n* (D9)
	Sb^{122}	A	β^-	2.8 days (L28)	0.81, 1.64 (A10, M35) cl. ch. and abs.	0.96 (M35) coincid abs.	Sb-*d*-*p* (L18) Sb-*n*-γ (A1, L18) Sn-*d*-2*n* (L18) Sn-*p*-*n* (D9)
	Sb^{124}	A	β^-	60 days (L18)	1.53 (M35) abs.	1.82 (M35) coincid. abs.	Sb-*d*-*p* (L18) Sb-*n*-γ (L18) I-*n*-α (L18)
	Sb<^{126}	D	β^-	3 hr. (L18)			Sn-*d*-*n* (L18)
	Sb<^{126}	D		~45 days (L18)			Sn-*d*-*n* (L18)
	Sb<^{126}	D		~2 yr. (L18)			Sn-*d*-*n* (L18)
	Sb^{127}	A	β^-	80 hr. (A6)			U-*n* (A6)
	Sb^{129}	A	β^-	4.2 hr. (A6)			U-*n* (A6)
	Sb>^{131}	D	β^-	<10 min. (A6)			U-*n* (A6, S21) Th-*n* (S21)
	Sb>^{131}	D	β^-	<10 min. (A6)			U-*n* (A6)
	Sb>^{131}	D	β^-	5 min. (A6)			U-*n* (A6)
52	Te^{121}	A	*K*, e^-	125 days (S15)			Sb-*d*-2*n* (S15) Sn-α-*n* (S15) Sb-*p*-*n* (S15)
	Te^{127}	A	*I.T.*, e^- (S15)	90 days (S15)		~0.10 (H25) spect. conv.	Te-*d*-*p* (S15) I-*n*-*p* (S15)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	A				Particles	γ-Rays	
52	Te^{127}	A	β^-	9.3 hr. (S15)			Te-*d*-*p* (S15, T4) I-*n*-*p* (S15) Te-*n*-2*n* (T4) Te^{127} (90 days) *I.T.* (S15) Sb^{127} β^- decay (A6)
	Te^{129}	A	*I.T.*, e^- (S15)	32 days (S15)		$\sim$0.10 (H25) spect. conv.	Te-*d*-*p* (S15, T4) Te-*n*-2*n* (T4)
	Te^{129}	A	β^-	72 min. (S15, A6)			Te-*d*-*p* (S15, T4) Te-γ-*n* (B20) Te-*n*-2*n* (H10, T4) Te^{129} (30 days) *I.T.* (S15) Sb^{129} β^- decay (A6)
	Te^{131}	A	*I.T.*, e^- (S15)	30 hr. (S15, A6)		0.17 (H25) spect. conv.	Te-*d*-*p* (S15) U-*n* (A6, H22)
	Te^{131}	A	β^-	25 min. (S15)			Te-*d*-*p* (S15) Te-*n*-γ (S15) U-*n* (A6) Te^{131} (30 hr.) *I.T.* (S15)
	Te$^{>131}$	D	β^-	43 min. (A6)			Sb$^{>131}$ (<10 min.) β^- decay (A6, H22)
	Te$^{>131}$	D	β^-	60 min. (A6)			Sb$^{>131}$ (<10 min.) β^- decay (A6, H22, S21)
	Te$^{>131}$	D	β^-	77 hr. (A6)			Sb$^{>131}$ (5 min.) β^- decay (A6, H22) Th-*n* (H24)
	Te$^{>131}$	D	β^-	$\sim$15 min. (S21)			U-*n* (S21) Th-*n* (S21)
53	I^{124}	A	β^+	4.0 days (L19, D9)			Sb-α-*n* (L19) Te-*p*-*n* (D9)
	I^{126}	A	β^-, γ	13.0 days (L19, T4)	1.1 (L19) abs.	0.5 (L19) abs. Pb	Sb-α-*n* (L19) I-*n*-2*n* (T4, L19) Te-*d*-*n* (L19) Te-*p*-*n* (D9)
	I^{128}	A	β^-, γ	25 min. (A1)	1.2, 2.1 (B19) cl. ch.	0.4 (L19) abs. Pb	I-*n*-γ (A1, T4) Te-*d*-2*n* (L19) Te-*p*-*n* (D9)
	I^{130}	A	β^-, γ	12.6 hr. (L19)	0.83 (T7) cl. ch.	0.6 (L19) abs. Pb	Te-*d*-2*n* (L19) Te-*p*-*n* (D9)
	I^{131}	A	β^-, γ	8.0 days (L19)	0.687 (T7) cl. ch.	0.4 (L19) abs. Pb	Te-*d*-*n* (L19) Te^{131} β^- decay (S15, A6 H22)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
53	$I^{>131}$	D	β^-	2.4 hr. (A6)			$Te^{>131}$ (77 hr.) β^- decay (A6, H22)
	$I^{>131}$	D	β^-	54 min. (A6)			$Te^{>131}$ (43 min.) β^- decay (H22, A6) Th-*n* (D6)
	$I^{>131}$	D	β^-	6.6 hr. (S21, D27)			$Te^{>131}$ (~15 min.) β^- decay (S21)
	$I^{>131}$	D	β^-	22 hr. (A6)			$Te^{>131}$ (60 min.) β^- decay (H22, A6, S21)
54	Xe^{127}	B	*I.T.* (?), e^-, γ (C41)	75 sec. (C41)		0.175, 0.125 (C41) spect. conv.	I-*p*-*n* (B41, C41)
	Xe^{127}	B	e^-, γ (C41)	34 days (C41)		0.9 (C41) abs. of e^-	I-*p*-*n* (C41)
	Xe^{139}	A	β^-	<0.5 min. (H28)			U-*n* (H28, H22, H11) Th-*n* (H29, A5)
	$Xe^{>131}$	D	*I.T.*, e^- (S27)	4.3 days (D27)		0.083 (H25) spect. conv.	$I^{>131}$ (22 hr.) β^- decay (S21, D27)
	$Xe^{>131}$	D		9.4 hr. (S21)			$I^{>131}$ (6.6 hr.) β^- decay (S21, D27)
	Xe	D	β^-	<0.5 min. (H28)			U-*n* (H28) Th-*n* (H29)
	$Xe^{>139}$	D	β^-	17 min. (G21)			U-*n* (H28, H22, G9, G21) Th-*n* (H29)
55	Cs^{134}	A	β^- (K25)	3 hr. (K25)	1 (K25) abs.		Cs-*n*-γ (A1, M16, K25) Cs-*d*-*p* (K25)
	Cs^{134}	A	β^-, γ (K25)	1.7 yr. (K25)	0.9 (K25) abs.		Cs-*n*-γ (A8, S20, K25) Cs-*d*-*p* (K25)
	Cs^{139}	A	β^-	7 min. (H28)			Xe^{139} β^- decay (H28, H22, H11)
	Cs	D	β^-	40 sec. (H28)			Xe (<0.5 min.) β^- decay (H28)
	$Cs^{>139}$	D	β^-	33 min. (H28)	2.6 (G21) abs.		$Xe^{>139}$ (17 min.) β^- decay (H28, H22, G9, G21) Pa-*n* (G7)
56	Ba^{133}	A	e^-, γ	30 hr. (K25)		0.30 (D9) spect. conv.	Ba-*n*-2*n* (K25) Cs-*p*-*n* (D9)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
56	Ba^{139}	A	β^-	86 min. (P8, H28)	1 (K25) abs.	0.6 (K25) abs. Pb, Cu	Ba-*d*-*p* (P8, K25) Ba-*n*-γ (A1, P2) La-*n*-*p* (P8) Cs^{139} β^- decay (H29, H22, H11)
	Ba	D		3 min. (A1, P2)			Ba-*n*-? (A1, P2, K25)
	Ba	D	β^-	~300 hr. (H28, G21)			Cs (40 sec.) β^- decay (?) (G21)
	Ba$^{>140}$	D	β^-	14 min. (H28, H22)			U-*n* (H28, H22) Th-*n* (H15, H14)
	Ba$^{>140}$	E	β^-	<1 min. (H14)			U-*n* (H14)
57	La^{138}	F		2.2 hr. (P2)			La-*n*-2*n*(?) (P2)
	La^{140}	A	β^-	31 hr. (P9)	0.8 (P9) cl. ch.		La-*d*-*p* (P8) La-*n*-γ (P9, M13)
	La$^{>140}$	D	β^-	2.5 hr. (H28, H22)			Ba$^{>140}$ (14 min.) β^- decay (H28, H22, H14) Th-*n* (C16)
	La$^{>140}$	E	β^-	<30 min. (H14, H15)			Ba$^{>140}$ (<1 min.) β^- decay (H14, H15)
	La	D	β^-	36 hr. (H28)			Ba (~300 hr.) β^- decay (H28, H22, G21)
58	Ce^{139}	F	β^+	2.1 min. (P9)			Ce-*n*-2*n*(?) (P9)
	Ce^{141,143}	C		15 days (R11)	0.12 (R11) spect.		Ce-*n*-γ (R11)
59	Pr^{140,142}	C	β^+	3.5 min. (P9)			Pr-*n*-2*n* or Pr-*n*-γ (P9, A1)
	Pr^{142}	A	β^-	18.7 hr. (P9)			Pr-*n*-γ (P9, P2, M13, A1) Nd-*n*-*p* (P9, P2)
60	Nd^{147}	E	β^-	84 hr. (P9)			Nd-*d*-*p* (P9) Nd-*n*-γ (P9) Nd-*n*-2*n*(?) (P9)
	Nd^{149}	E	β^-	2.0 hr. (P9)			Nd-*d*-*p* (P9) Nd-*n*-γ (P9) Nd-*n*-2*n*(?) (P9)
	Nd^{151}	E	β^-	21 min. (P9)			Nd-*n*-γ (P9, M13)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
61	61	F	β^-	12.5 hr. (P9)			Nd-*d*-*n* (P9)
62	Sm	D	β^-	21 min. (P9)			Sm-*n*-γ (P9, A1, M13, H17) Sm-*n*-2*n*(?) (P9)
	Sm	D	β^-	46 hr. (P9)			Sm-*n*-γ (P9, H20, R11, H17) Sm-*n*-2*n*(?) (P9)
63	Eu^{150}	E	β^+	27 hr. (P9)			Eu-*n*-2*n*(?) (P9, R11)
	$\text{Eu}^{152,154}$	C	β^-,γ,e^-(T6); *K*(?) (R2)	9.2 hr. (P9)	1.88 (β^-) (T6) spect.	0.123, 0.163, 0.725 (T6) spect. conv.	Eu-*n*-γ (P9, M13, H17, H20) Eu-*n*-2*n*(?) (P9) Eu-*d*-*p* (F7)
	$\text{Eu}^{152,154}$	C	β^-,γ (R11, F7)	>1 yr. (S20, F7)	0.8 (R11) spect.		Eu-*n*-γ (S20, R11, F7)
	$\text{Eu}^{152,154}$	E		12 min. (F7)			Eu-*d*-*p* (F7)
	$\text{Eu}^{152,154}$	E		105 min. (F7)			Eu-*d*-*p* (F7)
64	$\text{Gd}^{159,161}$	E		8 hr. (A1, H17)			Gd-*n*-γ (A1, H20, H17)
65	Tb^{160}	A	β^-	3.9 hr. (H16, M13)			Tb-*n*-γ (H17, P9, M13, H20)
66	Dy^{165}	A	β^-	2.5 hr. (H17, P9, M13)	1.9 (N4) cl. ch.		Dy-*n*-γ (H17, H20, P9, M13)
	Dy(?)	F	β^+	2.2 min. (P9)			Dy-*n*-? (P9)
67	Ho^{164}	F	β^-	47 min. (P9)			Ho-*n*-2*n*(?) (P9)
	Ho^{166}	B	β^-	35 hr. (H17)	1.6 (H20) abs.		Ho-*n*-γ (H17, H20, P9)
68	Er^{165}	F	β^+	1.1 min. (P9)			Er-*n*-2*n*(?) (P9)
	$\text{Er}^{169,171}$	C		7 min. (M13)			Er-*n*-γ (M13, M18)
	$\text{Er}^{169,171}$	C	β^-	12 hr. (H17, P9)			Er-*n*-γ (H17, H20, P9, R12)
69	Tm^{170}	A		105 days (H20)			Tm-*n*-γ (H20, N7)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	A				Particles	γ-Rays	
70	$Yb^{175,177}$	C		3.5 hr. (H17, M13)			Yb-*n*-γ (H20, H17, M13, P9)
	Yb(?)	G		41 hr. (P9)			Yb-*n*-γ(?) (P9)
71	$Lu^{176,177}$	C		4 hr. (H17, H20, M13)			Lu-*n*-γ (H20, H17, M13, M18)
	$Lu^{176,177}$	C		6 days (H17, H20, F6)			Lu-*n*-γ (H17, H20, F6)
72	Hf^{181}	A	β^-	55 days (H19)			Hf-*n*-γ (H19)
73	Ta^{180}	A		14–21 min. (B11, O1)			Ta-γ-*n* (B11) (Ta-*n*-2*n*)(?) (O1)
	Ta^{180}	A	*K* e^-, γ (O1); β^-(?)	8.2 hr. (O1)	<0.5(e^-)? (O1) abs.		Ta-*n*-2*n*(O1, P2)
	Ta^{182}	A	β^-	97 days (O1)			Ta-*n*-γ (O1, F6) Ta-*d*-*p* (O1)
74	W^{185}	B	β^-, γ (M36)	77 days (M36)	0.4–0.5 (M36) abs.		W-*n*-γ (M36) W-*n*-2*n* (M36)
	W^{187}	B	β^-, γ (M36)	23 hr. (M14)	1.1 (M36) abs.		W-*n*-γ (M14, A1, M36)
75	Re	E	β^+ (C42)	41–55 min. (C42, D9)			W-*p*-*n* (D9, C42)
	Re	E		13 min. (C42)			W-*p*-*n* (C42)
	Re	E	*K*(?), γ (C42)	>40 days (C42)			W-*p*-*n* (D9, C42)
	Re^{186}	B	β^-	90 hr. (S16)	1.05 (Y4) cl. ch.	No γ (C42)	Re-*n*-γ (S16, K7, Y4) Re-*n*-2*n* (S16, Y4) W-*p*-*n* (D9, C42)
	Re^{188}	B	β^-	18 hr. (P2)	2.5 (S16) cl. ch. (K.U.)		Re-*n*-γ (P2, K7, S16, Y4)
76	$Os^{191,193}$	C	β^-	40 hr. (K7)			Os-*n*-γ (K7)
77	$Ir^{192,194}$	C	β^-	1.5 min. (M15)			Ir-*n*-γ (M15)

TABLE 2—*Continued*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	*A*				Particles	γ-Rays	
77	$Ir^{192,194}$	C	β^-	19 hr. (M15, A1)	2.2 (A2) spect.		Ir-*n*-γ (M15, A1, P2, J4) Au-*d*-α, *p*(?) (C18)
	$Ir^{192,194}$	C	β^-	60 days (M15, F6)			Ir-*n*-γ (M15, F6, J4)
78	Pt^{197}	B	β^-	18 hr. (M15)			Pt-*n*-γ (M15) Pt-*d*-*p* (C19)
	Pt^{197}	B	β^-	3.3 days (M15)			Pt-*n*-γ (M15, P2)
	Pt^{199}	A	β^-	31 min. (M15)			Pt-*n*-γ (M15, A1, M14) Pt-*d*-*p* (C19)
79	Au^{196}	B	β^-	13 hr. (M15)			Au-*n*-2*n* (M15)
	Au^{196}	B	β^-, γ	4–5 days (M15)	0.36 (C43)	0.41 (C43)	Au-*n*-2*n* (M15)
	Au^{198}	A	β^-, γ	2.7 days (M15, A1)	0.8 (M15, R2) abs. and cl. ch.	0.28, 0.44, 2.5 (R2, S17) cl. ch. recoil	Au-*n*-γ (M15, A1, P2) Au-*d*-*p* (C18)
	Au^{199}	A	β^-	3.3 days (M15)			Pt^{199} β^- decay (M15)
80	Hg^{197}	B	*K*, e^-, γ (R11, A4)	43 min. (H10, M15)	<0.4 (M15) abs.	<0.25 (M15) abs.	Hg-*n*-2*n* (M15, H10, P2)
	$Hg^{203,205}$	C		25 hr. (M15)			Hg-*n*-γ (M15, A9)
81	Tl^{200}	F		4 min. (K3)			Au-α-*n*(?) (K3)
	Tl^{200}	F		3.8 hr. (K3)			Au-α-*n*(?) (K3)
	Tl^{204}	B	β^-	4.23 min. (F17)	1.6 (F17) abs.	No γ (F17)	Tl-*n*-γ (P10, P2, H10) Tl-*d*-*p* (F17) Tl-*n*-2*n* (F17, P2, H10)
	Tl^{206}	B	β^-	1–2 yr. (F17)			Tl-*n*-γ (F17) Tl-*d*-*p* (F17)
82	Pb^{205}	B		80 min. (D10)			Pb-*n*-2*n* (D10)
	$Pb^{204*, 206*}$	C	*I.T.* (?) e^-, γ	52 hr. (F17)		~0.5 (F17) abs. of e^-	Tl-*d*-*n* (F17)
	Pb^{209}	B	β^-	3.0 hr. (T5)			Pb-*d*-*p* (T5)
	Pb^{*}	D	*I.T.*, e^-	1.6 min. (W27)		~0.3 (W27) abs. of e^-	Pb-x-rays (W27)

* Radioactive isomer of stable nucleus.

TABLE 2—*Concluded*

RADIOELEMENT		CLASS	TYPE OF RADIATION	HALF-LIFE	ENERGY OF RADIATION IN MEV.		PRODUCED BY
Z	A				Particles	γ-Rays	
83	Bi^{210}	A	β^-	5 days (L13)			Bi-*d*-*p* (L13, C26, H27) Bi-*n*-γ (M29)
84	Po^{210}	A	α	136 days			Bi^{210} β^- decay (L13, C26, H27) Bi-*d*-*n* (V4, C26, H27)
	Po^{211}	A	α	~10^{-3} sec. (C46, C23)	7.5 (C46, C23) abs.		85^{211} *K* decay (C46, C23)
85	85^{211}	A	α, *K*	7.5 hr. (C46, C23)	6(α) (C46, C23) abs.		Bi-α-2*n* (C46, C23)
90	UY^{231}	B	β^-	24.5 hr. (N5)			Th-*n*-2*n* (N5)
	Th^{233}	A	β^-	26 min. (M17)			Th-*n*-γ (M17)
91	Pa^{233}	F	β^-	25 days (M17)			Th^{233} β^- decay(?) (M17)
92	U^{239}	A	β^-	23 min. (I1, S4)			U-*n*-γ (H18, H14, I1, M19)
	U^{237}	B	β^-, γ (M37)	~7 days (M37, N8)	0.26 (M37) abs.		U-*n*-2*n* (M37, N8)
93	93^{239}	A	β^-	2.3 days (M28, M19)	0.47 (M28) abs.	0.22, 0.27 (H25) spect. conv. and spect.	U^{239} β^- decay (M28)

as possible. References to the original discoveries are not given when better data are available in more recent publications. The references which are listed usually give a key to the complete literature.

The half-lives of H^3, Be^{10}, and C^{14} have been estimated from the measured intensities of the radioactivities together with reasonable assumed values for the yields.

VII. APPLICATIONS TO CHEMISTRY

Some of the applications of artificial radioactivity which have been made to chemistry are described in this section. The use of the natural radioelements as "indicators" or "tracers" in physical and chemical investigations has found a wide application. Descriptions of the methods and the types of problems which have been solved may be found in the books written by Hahn (H39), Paneth (P12), and Hevesy and Paneth (H50). The treatises on radioactivity by Curie (C38) and Meyer and Schweidler (M32) also contain discussions of such problems. These investigations were limited to those few elements which have naturally occurring radioactive isotopes. Those elements which exist both in the form of a stable type and as radioactive isotopes, such as lead (ThB), bismuth (ThC), and thallium (ThC″), are particularly suited to investigations of this kind. The "tagging" of atoms (for example, hydrogen, carbon, nitrogen, and oxygen) has also been accomplished by the use of separated (inactive) isotopes. This method, which is applicable in principle to any element which has two or more separable isotopes, has led to the solution of a large number of problems; an excellent review of this work was written in 1939 by Reitz (R22).

The large number of artificial radioactivities now known (about three hundred and fifty) makes it possible to extend the powerful radioactive indicator method to nearly every element. Although there is at least one radioactive form of every element, the restrictions imposed by the half-life, which must be sufficiently long for convenient manipulation, prevent the use of some of the radioactivities.

The application of the indicator method, by the use of the artificial radioelements, has also been made to the fields of physiology, zoology, biology, biochemistry, physics, medicine, and botany. Only the applications to chemistry will be discussed in this review. Hevesy has written a review article on the application of radioactive indicators in biology and biochemistry, which will appear in the *Annual Reviews of Biochemistry* for 1940.

The discussion of the applications which is to be given in this section, although not detailed, should reveal the type of information that can be obtained by application of the radioactive method and should give a key to the literature on the subject. Whenever it is necessary in this discussion to designate a radioactive form of an element in a chemical equation, this will be done with the aid of an asterisk; for example, bromide ions which have been "labelled" as the result of the presence of radioactive bromide ions will be written Br^{-*}. (The asterisk as used in table 2 has another meaning,—namely, to denote radioactive isomers of stable nuclei. It is not likely that this usage, which is in conformity with the practice of nuclear physics, will give rise to confusion.)

1. Exchange reactions

Perhaps the most extensive chemical application of the artificial radioelements as indicators has been to the study of "exchange reactions."

The first exchange experiments were performed by Hevesy and coworkers (H56), who used the natural radioactive lead isotope ThB to demonstrate a rapid exchange between the lead atoms in aqueous lead nitrate and lead chloride and also between plumbous and plumbic acetates in acetic acid solution. Reitz (R22) and Rosenblum and Flagg (R20) have written reviews (1939) on the applications of artificial radioelements for the measurement of exchange reactions. Exchange reactions were discussed also by Brejneva and Roginsky (B49). In exchange experiments the atoms of an element, in one of its valence forms or types of chemical combination, are "labelled" by admixture with some radioactive isotope of the element which is in the same form of chemical combination. To this system is added the element in another state of valence or form of combination (containing none of the radioactive isotope); the presence of radioactivity in this second chemical form, after it has been separated from the first, shows that an effective exchange of atoms between the two different states of the element has taken place. Complete exchange has been attained when the radioactivity has distributed itself between the two chemical forms in the same ratio as the amounts of the element in the two forms, that is, when the specific activity is the same. In all exchange reactions, regardless of the order, the rate varies with time according to the law for first-order reversible reactions, since the chemical composition of the reaction mixture remains unchanged (M34).

The following description of exchange work should serve to illustrate the type of information which can be obtained from such experiments. For example, these experiments give information on chemical bond types, the strength and reactivity of chemical bonds and the effect of solvents on these properties, the reactivities of ions and compounds, the structure of ions and compounds, the mechanism of reactions, and the mechanism of catalysis. In addition, exchange reactions often offer an excellent and convenient method for the introduction of radioactive atoms into compounds.

The experiments of several groups of investigators have shown that the thermal exchanges between halogens and the corresponding halide ions in aqueous solution at room temperature are practically instantaneous. Radioactive Cl^{38}, Br^{80}, Br^{82}, and I^{128} were used as indicators. Long and Olson (L39) were able to show, by means of a method of competing reactions, that radiochlorine and chloride ion, in acidified aqueous solution, undergo an extremely fast exchange, and Halford (H58) has pointed out that their results, taken together with other data, show that the half-life for the exchange is less than 10^{-4} sec. for 1 *M* Cl^-. Roginsky and Gopstein (R21) and Dodson and Fowler (D18) showed that the bromine–bromide exchange is very rapid in aqueous solution, while Hull, Shiflett, and Lind (H40), Juliusberger, Topley, and Weiss (J1), and Dodson and Fowler (D18) showed that the same is true for the iodine–iodide exchange. Topley and Weiss (T9) have shown that bromine and hydrobromic acid exchange bromine atoms rapidly also in dry carbon tetrachloride at room temperature, and Libby (L55) has shown that iodine and antimony triiodide undergo exchange within 20 min. in dry pentane at 37°C.

Brejneva, Roginsky, and Schilinsky (B34) found complete exchange at room temperature within 10 min. between *solid* aluminum bromide (Al_2Br_6) and either gaseous bromine or hydrogen bromide. Exchange experiments between gaseous bromine and solid cupric bromide led Roginsky and Gopstein (R21) to the unexpected conclusion that the two bromine atoms in solid cupric bromide are not equally reactive. Kolthoff and O'Brien (K20) found an exchange, more than 50 per cent complete in 100 min. at room temperature, between bromine gas and solid silver bromide.

Hull, Shiflett, and Lind (H40) showed that there is no very rapid exchange between iodine and iodate ion in 1 *N* sulfuric acid solution. The experiments of Libby (L43) show that there is no appreciable rate of exchange at room temperature between perchlorate ion and chlorate ion or between perchlorate ion and chlorine or chloride ion in either acid or alkaline solution. He finds that chlorate and radiochlorine exchange at a measurable rate in acid solution, the half-time of the reaction being about 95 min. in 1 *M* sodium chlorate and 2 *M* sulfuric acid. Libby (L43) and Rollefson (R24) found that bromate and bromine exchange at a faster rate in acid solution, while Kennedy (K17) and Libby (L43) used radioactive I^{131} to show that iodate and iodine exchange in acid solution. According to Libby (L43), the exchange rates seem to increase in the same order as the ordinary reactivities of the halate ions. Polessitsky (P17) found that bromate and bromide, as well as iodate and iodide, do not exchange even after hours at 100°C. (presumably in slightly alkaline solution).

It has been found by many investigators (S28, H40, M24), using radioactive Cl^{38}, Br^{80}, Br^{82}, and I^{128} as indicators, that the non-ionizing alkyl halides (as well as the alkyl dihalides, haloforms, and tetrahalides) do not undergo thermal exchange at any appreciable rate at room temperature with free halogens or halide ions. Szilard and Chalmers (S28), who were probably the first to make this observation, irradiated with neutrons compounds such as ethyl iodide and bromoform, from which they separated the radioactive atoms in concentrated form as silver halides. For iodine and either methyl iodide (M24) or ethyl iodide (H40) exchange was not observed even after about 15 min. at 90–100°C. However, exchanges of this type do take place when certain solvents are used for the mixtures of alkyl halides and inorganic halides or halogens. McKay (M24) and Juliusberger, Topley, and Weiss (J1) found that iodide undergoes rapid exchange (1 to 2 min.) with methyl iodide at room temperature in ethyl alcohol (J1, M24), acetone (M24), or amyl alcohol (M24). When iodine was substituted for iodide, the exchange required an elevated temperature (M24); complete exchange occurred in alcohol after 15 min. at 100°C. However, McKay (M24) and Juliusberger, Topley, and Weiss (J1) did not observe exchanges at room temperature between iodide and ethyl, *n*-propyl, isopropyl, and methylene iodides in ethyl alcohol or between iodide and iodoform in acetone; McKay (M24) found that all of these exchanges did occur within 15 min. in solvents at 100°C. Hull, Shiflett, and Lind (H41) also showed that the exchange between iodide and ethyl iodide in alcohol was slow at room temperature and very rapid (< 1 min.) at 100°C. There is a pronounced difference between the behavior of methyl iodide and the other alkyl halides in these experiments.

McKay (M24) has demonstrated that phenyl iodide, *p*-nitroiodobenzene, and *p*-iodoaniline do not exchange with iodide at 100°C. in ethyl alcohol, and it was shown by Friedmann, Solomon, and Werthessen (F10) that the bromine atoms of phenyl bromide and sodium bromide do not interchange. Juliusberger, Topley, and Weiss (J2) showed that only the negative, ionizing iodine of diphenyliodonium iodide exchanges with iodine in a water–alcohol mixture at room temperature.

Brejneva, Roginsky, and Schilinsky (B34, B35) found in a detailed study that the very reactive reagent aluminum bromide, at room temperature with no auxiliary solvent, did rapidly exchange bromine atoms with certain alkyl bromides, benzyl bromide, and all the bromines in certain alkyl polybromides; the exchange also occurred with the aromatic bromides, but was much slower. These experiments give important information on the strength of a number of bromine–carbon bonds. They also observed a fast exchange between aluminum iodide and ethyl iodide, and suggest that the use of radioactive aluminum halides should offer a general convenient method for the synthesis of radioactive organic halides. The radioactive aluminum halide can be prepared by taking advantage of the complete exchange between solid aluminum halide and gaseous radioactive halogen or hydrogen halide. In a later communication Brejneva, Roginsky, and Schilinsky (B46) show that, although two alkyl bromides do not undergo exchange alone, the presence of aluminum bromide effects exchange according to the following mechanism:

$$RBr^* + AlBr_3 \rightleftarrows RBr + AlBr_2Br^*$$

$$R'Br + AlBr_2Br^* \rightleftarrows R'Br^* + AlBr_3$$

$$RBr^* + R'Br \rightleftarrows R'Br^* + RBr$$

In the presence of aluminum bromide and no auxiliary solvent, exchange between the pairs ethylene dibromide and ethyl bromide, bromoform and ethyl bromide, amyl bromide and ethyl bromide reached practical completion in experiments of 45 min. duration.

Some thermal and photochemical exchange reactions of bromine have been studied by Wilson and Dickinson (W22). They found a rapid thermal exchange (within 10 min.) between radioactive bromine and either arsenious bromide or stannic bromide at room temperature in carbon tetrachloride solution. In the same solvent no thermal exchange was observed to occur between radioactive bromine and either ethylene dibromide (65 min.) or trichlorobromomethane (40 min.) in the dark at 100°C., but a rapid exchange (practically complete in 20 min.) between bromine and trichlorobromomethane is induced by green light at 76°C.

Grinberg and Filinov (G20) showed that radioactive bromide ions in aqueous solution at room temperature undergo complete exchange with the four bromine atoms of K_2PtBr_4 and the six bromine atoms of K_2PtBr_6. They state that this probably means that the six positions of the bromines in the octahedron of $PtBr_6^{--}$ are equivalent. Polessitsky (P17) performed exchange experiments to demonstrate the equivalence of the four iodine atoms in K_2HgI_4.

Brejneva, Roginsky, and Schilinsky (B34) used radiobromine to show that gaseous bromine and hydrobromic acid undergo complete exchange within 15 min. at room temperature. In a more detailed investigation Liberatore and Wiig (L45, L46) showed this exchange to be homogeneous and non-photochemical in character and almost complete within 2 min. As a mechanism they suggest a chain involving bromine atoms reacting according to

$$\mathrm{Br} + \mathrm{HBr}^* = \mathrm{HBr} + \mathrm{Br}^*$$

and

$$\mathrm{Br} + \mathrm{BrBr}^* = \mathrm{BrBr} + \mathrm{Br}^*$$

followed by similar reactions of Br* with hydrogen bromide and bromine, and they suggest that the primary bromine atoms are produced in the ionization processes associated with the radioactive bromine radiations. Libby (L47) also observed a fast exchange, and he suggests as an alternative mechanism a direct bimolecular reaction between bromine and hydrogen bromide through an HBr_3 complex. The question of the mechanism has not yet been settled. Libby (L47) found that iodine and hydroiodic acid undergo exchange either in the gaseous state or in dry pentane.

Liberatore and Wiig (L46) showed that gaseous hydrogen bromide and ethyl bromide do not undergo exchange at room temperature even when exposed to the full light of a 500-watt tungsten lamp for 9 hr. However, rapid thermal exchange takes place when hydrogen bromide and ethyl bromide are heated to 200–300°C., and they suggest as an explanation the equilibrium $C_2H_5Br = C_2H_4 + HBr$.

Ruben, Norris, and Nahinsky (R31) used radioactive C^{11} to show that there is no exchange between gaseous carbon dioxide and carbon monoxide within 1.5 hr. at 200°C.

Andersen (A3) used radioactive S^{35} (88 days half-life) to demonstrate that there is no exchange between the two sulfur atoms in thiosulfate ion, and thus proved that the sulfur atoms in thiosulfate are not equivalent. Voge and Libby (V8) and Voge (V6) have also used the radioactive S^{35} to study the exchange of sulfur atoms between various valence forms of sulfur in aqueous solution. They found that an exchange took place (within the time taken for the experiment, 1 hr.) in polysulfide at 100°C., thus demonstrating a probable equivalence of the sulfur atoms in the polysulfide ion. They also observed a much slower exchange of sulfur atoms between sulfide ion and thiosulfate ion (after about 20 hr.) at 100°C. Their experiments showed that there is no appreciable exchange between sulfide ion and sulfate ion in alkaline solution or between sulfite and sulfate in either alkaline or acid solutions, even after 36 hr. at 100°C. They showed that there is no exchange of sulfur between aqueous thiosulfate and sulfite within 20 hr. at 20°C., but thiosulfate and sulfite completely exchange one sulfur within an hour at 100°C. This is in agreement with the results of Andersen concerning the non-equivalence of the two sulfur atoms in thiosulfate. Gaseous sulfur dioxide and sulfur trioxide did not exchange at temperatures appreciably below those at which dissociation of the trioxide might be expected. Cooley, Yost, and McMillan (C25) have shown that no exchange occurs when elementary sulfur is dissolved in carbon disulfide and the solution kept at a temperature of 100°C. for 68 hr.

The exchange reactions of manganese in its various valence states in aqueous solution have been investigated by Polissar (P13), who used the radiomanganese (Mn^{56}) of 2.6 hr. half-life as indicator. His experiments showed that manganous ion and manganic ion (present as the manganic oxalate complex ion), undergo a rapid and complete exchange. He found that there was no rapid exchange between the following pairs of valence states: (*a*) permanganate ion–manganous ion, (*b*) permanganate ion–manganic ion (oxalate complex), (*c*) permanganate ion–manganese dioxide (solid), and (*d*) manganous ion–manganese dioxide (solid). Libby (L43) found a very rapid exchange at room temperature between manganate and permanganate ions; it seems certain that the mechanism involves an electronic exchange between the two ions.

Perrier and Segrè (P14) used the 14.3-day radiophosphorus (P^{32}) to investigate the possibility of an exchange between phosphate and hypophosphite in aqueous solution. Their experiments showed that there was no exchange either during 10 days at room temperature or 24 hr. at 100°C. in neutral or acid solution. Wilson (W18) showed that there is no exchange between phosphate and phosphite either in acid or alkaline solution within 1 day at 100°C., or in acid solution after 26 days at 25°C. His results also showed that, if the phosphorus atoms in hypophosphoric acid ($H_4P_2O_6$) are equivalent, the equilibrium constant for the formation of hypophosphoric acid from phosphorous and phosphoric acids is less than 8×10^{-5} (mole^{-1} liters) at 25°C. in 5.6 *M* hydrochloric acid.

Wilson and Dickinson (W19) used radioarsenic (As^{76}, 26 hr. half-life) to show that arsenate and arsenite do not exchange, in either acid or alkaline solution, even after 3 hr. at 100°C.

Some exchange reactions of iron were studied by Kennedy, Ruben, and Seaborg (K15), who used Fe^{59} (47 days) as indicator. They studied oxidation–reduction exchanges and found that ferrous and ferric ions undergo instantaneous exchange ($<$ 10 sec.) in 6 *N* hydrochloric acid solution at room temperature, while ferrocyanide and ferricyanide ions do not exchange in slightly acid or slightly alkaline solution within 3 days at room temperature. Ferric ion and ferricyanide ion do not exchange. Likewise, no exchange of iron atoms occurs in precipitates of either Prussian blue or Turnbull's blue. Ruben and Nahinsky (R31) used the 43-min. Hg^{197} to show that mercurous and mercuric ions undergo rapid exchange in aqueous solution at room temperature.

Ruben, Kamen, and Frenkel (R32) have employed the 10.2-min. Mg^{27} to study the nature of the magnesium bonds in chlorophyll. There was no exchange in 40 min. at room temperature between Mg^{++} and highly purified samples of either chlorophyll *a* or chlorophyll *b* in a buffered 80 per cent acetone solution. The exchange between Mg^{++} and the magnesium compound of 8-hydroxyquinoline proceeds rapidly in aqueous ethanol solution at room temperature. These investigators also used radioactive Fe^{59} to show that there is no exchange between Fe^{+++} and ferrihemoglobin in aqueous solution or between Fe^{+++} and ferriheme in ethanol at room temperature even in experiments lasting several weeks. Since it is known from magnetic susceptibility measurements (P20) that the iron in both of these molecules is held by ionic bonds, it seems that the highly symmetrical electrostatic field of the porphin ring is sufficiently strong to prevent any reversible equilibrium involving the central metal ion.

A few solid-phase–liquid-phase exchange reactions have been studied. Rollin (R26) has investigated the exchange between metals and their ions in aqueous solution. In a qualitative experiment he found appreciable exchange when inactive zinc metal, in the form of a powder, was shaken for 1 hr. at room temperature with a solution of zinc chloride which contained radioactive Zn^{65} prepared by the deuteron bombardment of zinc. Also, Rollin used the 8.2-day Ag^{106}, prepared by the deuteron bombardment of palladium, to measure the exchange between metallic silver, in the form of a mirror on a glass surface, and silver ions in a silver nitrate solution. In some experiments the metal was labelled with the radioactive Ag^{106}, while in others the ions were radioactive. He found that exchange amounting to ten to one hundred atomic layers took place within an hour or two at room temperature. This seems to be explicable on the basis of a mechanism which involves local electrolysis caused by the existence of irregularities on the surface of the metal. Hevesy and Biltz (H49) had previously used a naturally radioactive lead isotope to demonstrate an exchange between metallic lead and a solution of plumbous salt in contact with it.

Kolthoff and O'Brien (K20) used the 4.4-hr. Br^{80} for the study of the exchange between bromine and solid silver bromide at room temperature with ethyl bromide as solvent for the bromine. They found that complete exchange occurs in a few hours with fresh silver bromide, and that the rate of exchange decreases when the age of the precipitate is increased, until finally no exchange occurs with drastically aged silver bromide. They also measured the exchange between radioactive iodine (using I^{128}) and fresh silver bromide with ethyl iodide as solvent for the iodine. In a similar manner Kolthoff and Yutzy (K19) measured the exchange between silver chloride and chloride ions, and Kolthoff and O'Brien (K21) and Polessitsky (P17, P18) measured the exchange between silver bromide and bromide ions in aqueous solution. Such experiments lead to the determination of the rates of aging of precipitates. Kolthoff and coworkers have previously applied naturally radioactive elements to problems of this type.

Although the subject of exchange reactions is too complicated to make accurate, complete generalizations possible, it seems profitable to make a few rough statements about homogeneous exchange reactions. If we consider exchanges of a given element between two sorts of molecules or ions in which it is held by electron-pair bonds to different numbers or kinds of other atoms, we may say in general that such exchange reactions do not proceed with appreciable rates except in those cases where there are reversible reactions which enable the exchanging atoms to reach equivalent states of chemical combination. For example, there is no exchange of atoms between phosphate and phosphite ions, sulfate and sulfite ions, sulfur and carbon disulfide, iodide ion and iodoform, etc. On the other hand, exchanges have been found between chlorine and chlorate ion (due to the oxidation–reduction equilibrium), between lead nitrate and lead chloride (an extreme example of the ionization exchange mechanism), and between iodide ion and iodine (through the formation of a symmetrical intermediate, I_3^-). Most of the homogeneous exchange reactions reviewed in this section may be classified as one of these particular types. When the two exchanging molecules differ only in their net charge, another exchange mechanism—the transfer of an electron from one to the other—may become possible. For example, exchanges have been observed between Fe^{++} and Fe^{+++} and between MnO_4^{--} and MnO_4^-. It is no doubt true that some exchanges occur through a simple transfer of atoms between molecules during a collision; such a mechanism is a special case of exchange through the formation of an intermediate. In many cases, the observation of exchanges of this sort suggests the existence of unstable intermediates which might not be known from other reaction studies.

2. *Study of reaction mechanisms*

The artificial radioelements offer a powerful tool for the study of rearrangements and reaction mechanisms in general. A few examples will serve to illustrate the type of problems which can be solved by this method.

Hughes, Juliusberger, Mastermann, Topley, and Weiss (H42) have used radioiodine (I^{128}) to make a careful measurement of the rate of exchange between iodide ion and *sec.*-octyl iodide in acetone solution. They showed that this rate was equal to the velocity of racemization of the *d-sec.*-octyl iodide by iodide ion under identical conditions and hence established in a direct way the fact that the inversion is preceded by a substitution, in agreement with the ideas of Olson and Long (O4). Hughes, Juliusberger, Scott, Topley, and Weiss (H43) employed the same method to prove that the racemization of α-phenylethyl bromide in the presence of bromide ion is preceded by a substitution.

Rollefson and Libby (R25) used radioactive Cl^{38} to study the nature of primary photochemical processes in solution. They use the fact that no exchange of chlorine atoms occurs within 30 min. at room temperature in an illuminated solution of radiochlorine in carbon tetrachloride to help them deduce that the high efficiency of photodissociation processes in solution is due to a high primary efficiency rather than to reaction of the dissociation products with the solvent. The availability of long-lived radioactive isotopes of antimony, tellurium, arsenic, zinc, etc. should make it possible to extend the scope and sensitivity of Paneth's mirror technique (P19) for the detection of free radicals. Leighton and Mortenson (L53) have already used the natural radioactive lead isotope RaD in an application of the highly sensitive radioactive method to test for free radicals in photochemical reactions.

Olson, Halford, and Hornel (O5) used radiochlorine to demonstrate that the rearrangement of *N*-chloroacetanilide to *o*- and *p*-chloroacetanilide proceeds, not by means of an intramolecular rearrangement, but through a mechanism which involves a chlorine intermediate. Long (L40) was able to show that the racemization of chromioxalate ion, $Cr(C_2O_4)_3^{---}$, does not proceed through an ionization mechanism, since his experiments with radiocarbon (C^{11}, 21 min. half-life) showed that there is no exchange between oxalate ion and chromioxalate ion. Ettle and Johnson (E12) used radioactive Cl^{38} to show that the interconversion in aqueous solution of green 1:6-dichlorobisethylenediaminocobaltic chloride to the violet 1:2-isomer does not proceed by an intramolecular mechanism.

Wilson and Dickinson (W19), using the radioarsenic (As^{76}) of 26 hr. half-life, found a measurable rate of exchange between trivalent and pentavalent arsenic in acid solution in the presence of iodine and iodide ion. They used the radioactive indicator method to measure k and k' *at equilibrium* for the reaction

$$H_3AsO_3 + I_3^- + H_2O \underset{k'}{\overset{k}{\rightleftarrows}} H_3AsO_4 + 3I^- + 2H^+$$

and showed that the values which they obtained agreed with those obtained from measurements made far from equilibrium.

Experiments of the kind performed by Brejneva, Roginsky, and Schilinsky (B35) described above (study of aluminum bromide–organic bromide exchanges) should offer an insight into the mechanism of halogenation catalysis by substances of the aluminum bromide type. These same investigators (B44) made a detailed study of the kinetics of the aluminum bromide–ethyl bromide exchange reaction in carbon disulfide solution, where the rate is sufficiently slow for convenient measurement. They found an activation energy of 11 kg-cal. and favor a mechanism which involves the formation of an intermediate complex with the formula $RAlBr_4$.

Brejneva, Roginsky, and Schilinsky (B45) have mixed solutions of bromide ions in water and in ethyl alcohol in order to measure, with the aid of the 4.4-hr. Br^{80} and the 34-hr. Br^{82}, the rate of exchange between bromide hydrate and bromide alcoholate:

$$Br^-(H_2O)_n + Br^-(C_2H_5OH)_p \rightleftarrows Br^-(H_2O)_k(C_2H_5OH)_i$$

Surprising results were obtained. They found a rather slow rate; a time considerably longer than 10 min. was required for complete exchange at −31°C. Further experiments on this "inter-solvate" exchange were performed by Roginsky and Tartakovskaja (R30), who showed that chloride and iodide as well as bromide ions showed slow solvate exchange at room temperature for the following pairs of mixed solvents: methyl alcohol–water, acetone–water, glycerol–water, glycerol–acetone, and ethyl alcohol–water. Roginsky and Afanasiev (R35) have made a detailed study of the kinetics of this type of exchange, using bromide ions and water–acetone mixtures at temperatures of 0°, 16° and 32°C.

Le Roux and Sugden (L41) have used radioactive Br^{80} and Br^{82} to make a detailed study of the kinetics of the slow exchange of bromide ion and *n*-butyl bromide in aqueous acetone (90 per cent acetone by volume) over a range of temperatures from 0° to 65°C. Elliott and Sugden (E7) have extended these experiments to include three more alkyl bromides. The activation energies found are: *n*-propyl, 18.12; *n*-butyl, 18.87; isobutyl, 20.21; isopropyl, 22.94 kg-cal. The speed of these bimolecular reactions is of the same order of magnitude as that predicted for a gaseous system on the collision hypothesis; isopropyl bromide shows the highest value for the effective collision diameter.

Tuck (T10) has measured the rate of exchange of radioiodine (I^{128}) with tertiary butyl iodide in liquid sulfur dioxide under conditions which enabled him to deduce the velocity of electrolytic dissociation of the butyl iodide from the measurements.

It should be pointed out that the long-lived radiohydrogen (H^3) and radiocarbon (C^{14}) offer opportunities for the study of many very important reaction mechanisms, and a few such experiments are in progress at the present time.

3. *Reactions of high-energy atoms*

The work which has been done on the mechanism of the Szilard–Chalmers method of concentration and on the mechanism of the nuclear isomer separation method will be described in this section. This will include a discussion of the reactions and behavior of the atoms and molecules of very high energy which are formed as the result of neutron capture and isomeric transitions.

Szilard and Chalmers (S28) first demonstrated that a neutron-capture radioactivity can be very highly concentrated by suitable chemical methods. They irradiated ethyl iodide containing traces of iodine with neutrons and found that they could extract most of the radioactivity with water; this activity (I^{128}) was associated with an amount of iodine which was equivalent to only a small fraction of the total irradiated iodide. Later, Fermi and coworkers (A1) separated concentrated radioactive halides from neutron-irradiated halogenates and radioactive manganese dioxide (Mn^{56}) from irradiated potassium permanganate. D'Agostino (D19) studied these processes in more detail and also separated concentrated active arsenic (As^{76}) from irradiated cacodylic acid, $(CH_3)_2AsOOH$.

The formation of a radioactive isotope by neutron capture (the n,γ reaction) is accompanied by the emission of gamma-rays with an average energy of 3 to 6 Mev. (R23, F11, K16). The emission of a gamma-ray of energy E (Mev.) imparts a recoil energy of 535 E^2/M electron volts to an atom of atomic weight M when the nucleus of that atom captures a slow neutron. This energy, which, for example, amounts to about 100 electron volts in the case of manganese, is practically always sufficient to disrupt the molecule which contains the irradiated nucleus.

When the newly formed radioactive atoms are in, and remain in, a chemical form which is separable from the bulk of irradiated compound, there is obtained a high percentage of *extraction* of the radioactivity from, and hence small *retention* by, the irradiated compound. D'Agostino (D19), for example, found that he could extract as silver chloride practically 100 per cent of the 37-min. Cl^{38} when solid or aqueous sodium chlorate or perchlorate was irradiated with slow neutrons. He showed in similar experiments that there is also practically no retention of I^{128} by solid or neutral aqueous sodium iodate; the same is true for As^{76} when cacodylic acid is irradiated.

However, there are several factors which may act to decrease the percentage of extractable activity. The newly formed radioactive atoms may undergo thermal exchange (*cf.* section VII, part 1) with the inactive atoms in the irradiated compound and hence reënter the original form. Or the high-energy fragments which contain the radioactive recoil atoms may react while activated with surrounding molecules so as to form new molecules or re-form the irradiated molecules. The mechanism of the expulsion process and the reactions of such high-energy atoms have been the subject of rather detailed study by several groups of investigators.

Erbacher and Philipp (E8) studied the separation of radioactive halogens by aqueous extraction of irradiated alkyl halides. However, these investigators were only interested in obtaining the radiohalogens as free as possible from inactive halogens and did not make a detailed study of the efficiency of the extraction processes.

Glückauf and Fay (G16) have shown that the high-energy halogen atoms expelled by recoil from capture gamma-rays can frequently give rise to substitution products. They found, for example, dibromobenzene from irradiated bromobenzene, methylene iodide from methyl iodide, bromoform from methylene bromide, carbon tetrabromide from bromoform, etc. Identical yields of methylene iodide from irradiated methyl iodide were obtained over an extremely wide temperature interval (+15° to −195°C.), which shows that it is not an ordinary thermal reaction but rather a substitution of a hydrogen atom in methyl iodide by a high-energy recoil radioactive iodine atom. Considerable activity remains in the original methyl iodide, showing that the recoil iodine atoms can replace halogen as well as hydrogen. They also showed that the recoil halogens can replace hydroxyl, amino, carboxyl, and $-CH_2OH$ groups. That such reactions offer a method for the synthesis of concentrated radioactive halogen compounds is illustrated by the fact that practically pure radioactive phenyl iodide can be separated from methyl iodide irradiated in benzene solution.

The experiments of Lu and Sugden (L42) were designed with the view of finding methods for increasing the yield of extractable radioactive halogens from irradiated organic halides. They used, as extracting agents, acidic and alkaline aqueous solutions as well as finely divided metallic powders and metallic foils. With bromobenzene and iodobenzene the presence or absence of free halogen during irradiation has no effect; with the aliphatic halides the presence of halogen increases the percentage of extraction. Radioiodine is separable mainly as the free element; radiochlorine and radiobromine as anions. They found that a small amount of aniline present during the irradiation has a very marked effect in increasing the fraction of activity which can be extracted by acidified water. They suggest that this effect is explained by the reaction

$$R + X^* + NH_2C_6H_5 \rightarrow C_6H_5NH_2R^+ + X^{*-}$$

where R represents the highly energetic molecular residue which remains after the disruption of the molecule RX following the recoil of the radiohalogen X*. However, other explanations of this effect may also be advanced.

Libby (L43) has made a study of the reactions of the high-energy recoil atoms which result after the formation of radioactive Cl^{38}, Br^{80}, Br^{82}, I^{128}, P^{32}, Mn^{56}, and As^{76} by neutron capture. The halogenates show practically zero retention of activity in neutral or alkaline aqueous solution, while some retention occurs in acid solution. The time independence of the retention in the case of acid chlorate indicates that it is the high-energy recoils which are interchanging instantaneously to form radioactive chlorate. The increase of retention with increase of time between irradiation and extraction indicates that thermal exchange is occurring between acid bromate and iodate and their products (*cf.* section VII, part 1). Libby suggests that the retention of activity by the organic halides is best explained largely by the recombination of a stopped X* particle with its residual free radical or ion in the same reaction "cage." The lack of dependence upon environment in the case of the phosphate retention experiments (approximately 50 per cent of the activity extractable as phosphite in all cases) indicates that the initial recoil entirely determines the retention. The recoil products from irradiated permanganate undergo a wide range of follow reactions as determined largely by the environment. The remarkable complete retention of activity observed in the case of both arsenate and arsenite is explained on the basis of no change in valence during the recoil, followed by hydration reactions more rapid than any oxidation or reduction reactions with water. Suess (S48) studied the reactions of the high-energy bromine atoms formed as the result of neutron capture by gaseous ethyl bromide.

Another source of high-energy atoms is furnished by isomeric transitions. Segrè, Halford, and Seaborg (S10) first showed that the energy released during the radioactive transition from an upper to a lower isomeric state of a nucleus can be used to effect a chemical separation of two genetically related nuclear isomers. Subsequent work by Willard (W20) and Seaborg, Friedlaender, and Kennedy (S32) has shown that, for isomeric transitions, activation and bond rupture occur, not as the result of recoil energy (which is usually very small in isomeric transitions), but as a consequence of the high state of electronic excitation which results from the vacancy in the *K*- or *L*-shell created by the emission of the internal-conversion electron. Willard deduced this mechanism from the fact that isomeric transitions can initiate reactions which could not occur with energies as small as the recoil energies, while the other investigators were able to show that bond rupture occurs only when the transition gamma-rays are internally converted and not in the case of isomeric transitions with *unconverted* gamma-rays of even higher energy. Fairbrother (F12) also suggested this mechanism on the basis of experiments similar to those of Willard.

The radioactive isomeric transition from Br^{80} (4.4-hr. half-life) to Br^{80} (18-min. half-life) has been used to initiate a variety of chemical changes. Segrè, Halford, and Seaborg (S10) used this transition to activate the hydrolysis (or decomposition) of *tert.*-butyl bromide; Le Roux, Lu, and Sugden observed the decomposition of ethylene dibromide (L36, L42) and the hydrolysis (or decomposition) of *n*-butyl bromide (L36); DeVault and Libby (D12) observed the rupture of bromate ion; Fairbrother (F12) studied the decomposition of ethyl bromide. These reactions were all established by the presence of the 18-min. activity in the reaction products. Lu and Sugden (L42) found that the activated bromine from the decomposed ethylene dibromide reacts to some extent with metals, such as zinc powder and aluminum, copper and silver foil, as shown by the extraction of the 18-min. activity by these metals. Willard (W20) found that this transition activates bromine in such a way as to enable it to replace one of the chlorines in carbon tetrachloride; experiments over a wide range of temperature show the reaction to be independent of temperature, as should be expected. In a continuation of this work Willard (W23) has observed a wide range of reaction efficiencies for a number of reactions activated by this isomeric transition. He studied the reaction of bromine with ether and with mineral oil, the gas-phase decomposition of ethylene dibromide, the decomposition of ethyl bromide, the reaction of cinnamic acid dibromide with carbon tetrachloride, and the reaction of bromine with carbon tetrachloride in the presence of high concentrations of bromine. He observed no reaction of this nature between bromine and carbon tetrachloride in the gas phase.

Libby and DeVault (L52) observed reaction efficiencies ranging from 0 to 90 per cent (as measured by the amount of the 18-min. activity found in the reaction products) for a number of reactions activated by the Br^{80} isomeric transition. Decomposition reactions and reactions with solvents were studied. The experiments included observations on gaseous ethyl bromide, bromoform, and ethylene dibromide as well as ethyl bromide, bromoform, phenyl bromide, dibromopentane, and tertiary butyl bromide in various solvents. They suggest that their observed maximum reaction efficiency of 90 per cent corresponds to the internal-conversion coefficient for the Br^{80} isomeric transition. Imre (I2) has effected a separation of the Br^{80} isomers by means of an exchange experiment between bromide ions and solid silver chloride. Suess (S47) used the transition to activate the reaction between gaseous hydrobromic acid and acetylene.

As has already been mentioned, isomeric transitions in tellurium and selenium have been used to effect the reduction of tellurate to tellurite (S15) and selenate to selenite (L30). Seaborg, Friedlaender, and Kennedy (S32) found that the reduction of tellurate to tellurite proceeds with almost 100 per cent efficiency even when the solution is kept frozen at the temperature of liquid air. The decomposition of gaseous tellurium diethyl has also been observed (S32).

4. *Behavior of material at extremely small concentrations*

The use of radioactive isotopes in the absence of carrier material offers a unique method for the study of the behavior of substances at extremely small concentrations. Extensive applications of the natural radioelements to such problems have been described in the books of Hahn (H39), Paneth (P12), and Hevesy and Paneth (H50).

An indication of the type of experiments which can be performed has already been given in section II, where a description was given of the methods used for the isolation of radioactive transmutation products in the absence of carrier. Among the problems which can be investigated by this method there should be mentioned the measurement of the vapor pressure of non-volatile metals and other substances, the measurement of the absorptive power of solids for extremely small amounts of gases, the behavior of extremely small amounts of insoluble substances, electrodeposition and electrochemical deposition of extremely small amounts of material, the behavior of "radiocolloids," the behavior of fractionation processes at small concentrations, etc.

Grahame and Seaborg (G11) used radioactive Ga^{67}, Ga^{68}, Co^{56}, Mn^{56}, and Fe^{59} in order to measure at extremely small concentrations the distribution of the chlorides of these elements between ether and 6 N hydrochloric acid. They found distribution ratios identical with those at higher concentrations for all except ferric chloride.

Langsdorf and Segrè (L30) have used radioactive Br^{83} and Kr^{83} to study "emanation methods." By a technique which involved the introduction of the radioactive halogen into a silver-nitrate-impregnated silica gel they effected a very efficient emanation of the radioactive rare-gas decay product from the halogen. Hahn (H48) has discussed the diffusion rates out of uranium and thorium precipitates of the rare-gas radioactive fission products, xenon and krypton. Hahn and coworkers had previously applied this "emanation method," with the aid of the naturally radioactive rare gases radon and thoron, to a long series of investigations of the structure and the change of structure of solid substances (H39, Z1). Hahn (H48) points out that a comparison of the diffusion rates of krypton, xenon, and radon out of uranium and thorium precipitates should give the atomic weight dependence of the diffusion constants. A theoretical discussion of the emanation method and the information to be obtained from it is given by Flügge and Zimens (F15).

Seaborg, Kennedy, and Wahl (S33) used radioactive H^3 to study the thermal diffusion process in hydrogen at small concentrations. They showed that the isotope separation arrangement of Clusius and Dickel (C34) gives, at mole fractions as low as 10^{-12}, separation factors which are essentially the same as those obtained at much higher concentrations. Beams (B36) is also using radioactive H^3 in an investigation of the separation of isotopes by means of the ultracentrifuge.

An obvious application of the artificial radioelements will be to the problems of "radiocolloids" and colloid chemistry, which have been so extensively investigated with the natural radioelements (C36, C37). This has been the subject of a detailed treatment by Hahn (H39).

Another use of the artificial radioelements should be as indicators in the preparation of new compounds in a manner similar to Paneth's (P16) use of ThC (an isotope of bismuth) to demonstrate the existence of bismuth hydride.

5. *Analytical chemistry*

The artificial radioelements can be used as an aid in analytical chemistry in many ways:— to provide a method of analysis for the presence of certain elements, as a means of studying the completeness of chemical separations, as a means of studying coprecipitation problems, etc.

The presence of certain elements in a sample which is to be analyzed can often be established, with or without the help of a chemical separation, by means of their characteristic half-lives, after the substance has been activated in some manner. The analysis can often be made without destroying or even changing the form of the sample. A quantitative estimate of the amount of the element can be made in those cases where the yield of the reaction involving the formation of the radioactivity has been previously determined. Hevesy and Levi have applied this method of analysis to the rare-earth elements, where it is especially useful because of the extreme difficulty of application of ordinary analytical methods. In one experiment (H20) they found the 2.5-hr. dysprosium period in a sample of yttrium, after activation with neutrons, which showed the presence of dysprosium impurity to the extent of 1 per cent. Neutron activations of gadolinium samples (H19) were used as tests for small amounts of europium impurities by means of the 9.2-hr. europium period. Seaborg and Livingood (S38) bombarded a sample of iron with deuterons in order to establish, by means of the 20-min. Ga^{70} and 14-hr. Ga^{72} radioactivities, the presence of gallium impurity to the extent of 6 parts per million. They used this same method to demonstrate the presence of small amounts of copper in nickel, and of iron in cobalt, as well as of phosphorus and sulfur in various substances. King and Henderson (K9) were able to detect less than 1 part in 10,000 of copper in silver by bombarding the silver with alpha-particles. However, it must be pointed out that extreme care must be exercised in the application of these sensitive methods to analysis. This is especially true when a sample is bombarded with deuterons, protons, or alpha-particles, because of the danger that there might be introduced into the sample small amounts of impurities, from recoil atoms and volatilization, in the target chamber. Even when samples are bombarded through a window with the target outside of the acceleration apparatus, care must be taken to prevent the introduction of extremely small amounts of impurities during the preparation of the target.

Application of the radioactive method to the analytical problems of organic chemistry also shows some promise. Brejneva, Roginsky, and Schilinsky (B34) have pointed out that measurements on the rate of exchange with aluminum bromide should help one to trace the position of the bromine in the compound during the synthesis of complicated organic bromides. The aluminum bromide undergoes only a slow rate of exchange with bromine which is attached directly to the benzene or naphthalene rings, but exchanges quickly with aliphatic bromides and benzyl bromide.

Relative intensity measurements of induced radioactivity can be used for isotopic analysis of separated isotopes (K18).

The efficiency of separation processes in analytical chemistry can be tested with the help of radioactive indicators. This is a very convenient method, because the amount of a given element which remains in any fraction after a chemical separation can be quickly determined by means of its radioactivity. For example, Erbacher and Philipp (E9) used radioactive Au^{198} to study the completeness with which gold can be separated from platinum and iridium by a gravimetric procedure in which the elements are weighed after reduction to the metallic state. Saunders (S43) has used radioactive Te^{127} and Te^{129} to study, over a wide range of conditions, the amount of tellurium which is carried down with antimony when the antimony is precipitated as an oxide from a solution of boiling, concentrated nitric acid. Radioactive indicators have been used time after time in the chemical work connected with the Radiation Laboratory at Berkeley for the purpose of making quick, convenient, and effective tests of the efficiency of separation procedures in analytical chemistry.

Similarly it is possible to determine the solubility of very slightly soluble substances; for example, Ferla (F14) used radiophosphorus to study the completeness of precipitation of ammonium phosphomolybdate. Radioactive cobalt was used by Cacciapuoti and Ferla (C40) to measure the solubility in water of cobaltic hydroxide (5.6×10^{-3} mg. per liter).

Kolthoff and Yutzy (K19) have applied radioactive Cl^{38} to a measurement of the specific surface of a silver chloride precipitate by treating the solid with a solution of radioactive chloride ions and measuring the rate of exchange as a function of time. Kolthoff and O'Brien (K20, K21) and Polessitsky (P17, P18) have used the 4.4-hr. Br^{80} to study the surface and also the aging of silver bromide precipitates by means of exchange experiments.

6. *Chemical properties of rare elements*

The fact that extremely small amounts of radioelements can be detected by the radioactive methods makes it possible to use radioactive transmutation products to study the properties of elements which do not exist in nature or are so very rare that they have not yet been isolated. It must be emphasized that experiments of this type are performed with very small, unweighable amounts (approximately 10^{-10} g.) of the element, usually in the presence of foreign carrier material, and therefore the interpretation of the results, especially for precipitation processes, may sometimes be uncertain.

Perrier and Segrè (P15) were able to show that the deuteron bombardment of molybdenum produces radioactive isotopes of element 43, and they used these to study the hitherto unknown chemical properties of this element. Their experiments showed that the chemical properties resembled those of the heavier homolog, rhenium, to a much greater extent than they resembled those of manganese, the lighter homolog. They used rhenium as a carrier for the radioactivity in order to show that element 43 is precipitated by hydrogen sulfide from alkaline or acid (less than 10 *N*) solution. They investigated other properties, including the volatility of the oxide and chloride and the conditions for the electrolytic deposition of the metal. They worked out analytical procedures for the isolation of element 43 and specifically for its isolation from rhenium. Segrè (S36) has written a review of the known properties of the radioactive isotopes of element 43.

The recent discovery of radioactive element 85, from bismuth plus 32-Mev. alpha-particles, by Corson, MacKenzie, and Segrè (C23) makes possible an investigation of its properties. Segrè, MacKenzie, and Corson (S30, C46) have carried out an investigation of its chemical properties. The general behavior is that of a metal, with little resemblance to the other halogens. It is precipitated by hydrogen sulfide in 6 *N* hydrochloric acid solution with various carriers, and the sulfide is insoluble in ammonium sulfide. It is precipitated by stannous chloride in acid solution but not by sodium stannite in alkaline solution. Volatility at comparatively low temperatures is observed; a piece of bombarded bismuth loses most of the activity before melting (275°C.). There is no precipitation upon the addition of silver nitrate to a dilute nitric acid solution using iodide as carrier. Element 85 can be extracted with carbon tetrachloride with iodine carrier but with yields small compared with iodine under similar conditions. Worth mentioning here is the interesting observation of Hamilton and Soley (H44) that element 85 concentrates in the thyroid gland to an extent which has heretofore been peculiar only to iodine.

The decay scheme of element 85, which has a half-life of 7.5 hr. and probably has the mass number 211, is very interesting. The radioactive 85^{211} undergoes a branching decay, going to a bismuth isotope (Bi^{207}) by alpha-emission and to a polonium isotope (Po^{211}) by *K*-electron capture. The Po^{211} is the well-known naturally radioactive AcC′ and decays to stable Pb^{207} by alpha-particle emission with a half-life of 5×10^{-3} sec. The Bi^{207} probably also decays to Pb^{207}, since Bi^{207} does not exist in nature as a stable isotope, but as yet no radioactivity corresponding to this decay has been found.

The remarkable discovery by McMillan and Abelson (M28) that a 2.3-day activity, formed by the bombardment of uranium with neutrons, is an isotope of element 93 makes possible an actual investigation of the chemical properties of element 93. The properties of element 93 have been the source of much speculation for a long time. The 2.3-day activity was originally discovered by McMillan (M19), who found that this radioactive isotope is not found among the highly energetic recoil products which are formed when uranium undergoes neutron-induced fission. McMillan and Abelson have shown that this 2.3-day activity is the daughter of the 23-min. U^{239}, which is formed from U^{238} by the capture of slow neutrons, and hence must be assigned to the isotope 93^{239}. The radioactive 93^{239} decays by beta-particle emission to the isotope 94^{239}, and although it is probable that the isotope 94^{239} is radioactive, perhaps decaying by the emission of alpha-particles to the naturally radioactive U^{235} (actinouranium), McMillan and Abelson have shown that the half-life for alpha-decay of 94^{239} must exceed one million years.

A striking confirmation of the assignment of the 2.3-day activity to element 93 has been obtained in the physical measurements of Helmholz (H25). He placed a sample of the 2.3-day activity in an electron magnetic spectrograph and found electron lines corresponding to the internal conversion of gamma-rays in the *K*- and *L*-electron shells. Presumably these gamma-rays are emitted immediately following the beta-emission and hence the internal conversion occurs in element 94. Helmholz found that his measurements gave an energy difference of about 98 kilovolts between the *K*- and *L*-shells, which is very close to the difference expected for element 94. The corresponding difference between the *K*- and *L*-electron binding energy amounts to about 96 kilovolts in element 93 and about 94 kilovolts in uranium.

McMillan and Abelson have used this 2.3-day activity to investigate the chemical properties of element 93. They found that the chemical behavior of element 93 is much more similar to uranium than to its homolog, rhenium. For example, element 93 precipitates with sodium uranyl acetate, the reaction which is so characteristic of uranium. Likewise it precipitates with uranium in alkaline solution and redissolves upon the addition of ammonium carbonate, another reaction which is characteristic of uranium. Element 93 is not precipitated by hydrogen sulfide in dilute acid solution. It precipitates with the rare-earth elements, probably in the +4 oxidation state, upon the addition of fluoride or oxalate, and is chemically similar to the rare-earth elements in many other precipitation processes. The element also precipitates with insoluble iodates, a precipitation process which is characteristic of the +4 oxidation state of cerium and thorium. Chemical separation from the rare earths is effected by taking advantage of a higher oxidation state; for example, in the presence of bromate ions rare-earth precipitates do not carry the activity.

These chemical investigations with element 85 and element 93 have demonstrated that the chemical behavior of these elements differs rather markedly from that of their nearest homologs, iodine and rhenium.

Radioactive H^3, although not a new element as is the case for the other elements discussed in this section, will differ enough from hydrogen (H) and deuterium (D) in its chemical and physical properties to make an investigation of some of its properties worth while. Many investigations which have been based on differences in properties between hydrogen and deuterium can be extended to radioactive H^3 so as to obtain additional useful information. Such investigations include measurements of equilibrium constants of reactions and especially exchange reactions, reaction rate measurements which emphasize differences in the kinetic behavior of the three isotopes, determinations of the separation factors and efficiencies of isotope fractionation processes, study of diffusion and adsorption processes, etc. Some of these experiments would yield, for example, information on the zero point energy of the molecules HT and DT. (T is used here to represent radioactive H^3, triterium.) Of course the extent of such investigations would be limited, because H^3 is available only in very small, unweighable amounts. A detailed discussion of the investigations involving hydrogen and deuterium is given in the book written by Farkas (F16).

7. *Self-diffusion processes*

The radioactive indicator method has made it possible to measure the rate of diffusion of a substance into itself, that is, to measure the rate of "self-diffusion." For example, the radioactive lead isotopes (ThB and RaD) have been used to investigate the rate of self-diffusion in lead, both liquid and solid (H54, H55, G19). The discovery of artificial radioactivity extended the possibility for the application of this method to a large number of elements.

Sagrubskij (S39) and McKay (M27) have measured the rates of self-diffusion in gold at elevated temperatures. They activated gold with neutrons to form the radioactive gold (Au^{198}) of 2.7 days half-life and then measured the rate of diffusion of this radioactive gold through samples of ordinary inactive gold. As an example of the results obtained, McKay found the diffusion coefficient at 941°C. to be 9.7×10^{-6} mm.^{2} per minute. McKay found an activation energy of 51 kg-cal. per mole for this self-diffusion process.

Rollin (R27) and Steigman, Shockley, and Nix (S37) have used the radioactive copper (Cu^{64}) of 12.8 hr. half-life to measure the rate of self-diffusion in copper. Rollin, who activated the copper by direct bombardment with 8-Mev. deuterons, found that the diffusion coefficient at 940°C. is a few times smaller than that found by McKay at the same temperature for self-diffusion in gold. The results of Rollin show that the coefficient of self-diffusion in copper is smaller than might be predicted from the known rates of diffusion of several other elements in copper. His results gave an activation energy of 60 kg-cal. per mole for the self-diffusion process. Steigman, Shockley, and Nix electroplated the radiocopper, which was prepared by neutron bombardment of zinc, upon disks of inactive copper. They found an activation energy of 57.2 kg-cal. per mole and diffusion rates similar to those found by Rollin.

Banks and Day (B40) have measured the rate of self-diffusion in single crystals of metallic zinc. A thin deposit of radioactive Zn^{65}, obtained from copper by proton bombardment, was electrolytically deposited on a flat, polished, and etched surface of a single crystal of ordinary inactive zinc. They obtained, for example, a value at 400°C. of 5.17×10^{-5} mm.^{2} per minute for the diffusion coefficient parallel to the hexagonal axis. The value for the activation energy obtained by them is 17.6 kg-cal. per mole, a value which is much smaller than those found for the self-diffusion in gold and copper. Miller and Day (M26) measured the rates of self-diffusion in several samples of polycrystalline zinc. Their values for the diffusion coefficients, which were close to those found by Banks and Day, varied as much as 25 per cent among the various samples.

Jehle (J3) employed radioactive Na^{24} and Cl^{38} in measurements of the rate of self-diffusion of sodium and chloride ions in aqueous solution over a wide range of concentrations. His results at low concentrations are consistent with the known data on the diffusion coefficients of sodium chloride. Katzin (K13) is using radioactive Na^{24}, K^{42}, and Br^{82} to measure the rate of diffusion of sodium, potassium, and bromide ions through various membranes in the absence of concentration gradients.

8. *Experiments with radioactive carbon*

This section will describe the experiments which have been done with radiocarbon. Because of the special importance of carbon in chemistry, it seems desirable to discuss these experiments, in spite of the fact that most of them have been of a biochemical nature and this review has not included a discussion of the applications of artificial radioactivity to biochemistry. The experiments have been done with the 21-min. C^{11}, usually made by the deuteron bombardment of boron. The short half-life is an inconvenience, but the production of very intense activities by means of the cyclotron has made it possible to carry out experiments lasting as long as 5 hr. The production of the long-lived C^{14} of Ruben and Kamen (R17) will make it possible to perform experiments whose duration is not limited by the decay of the sample. However, radioactive C^{14}, which seems to be best prepared by the deuteron bombardment of the separated (or enriched) isotope C^{13}, has such a very long half-life that exceedingly long and intense bombardments are needed in order to obtain a radioactivity of sufficient intensity for useful work.

Ruben, Kamen, and Hassid (R33, R28) have been using radioactive C^{11} in a study of photosynthesis. Radioactive carbon dioxide was fed to the unicellar green algae *Chlorella* and also to higher plants under various controlled conditions in the light as well as in the dark. The results obtained so far have been rather surprising. The plants and the algae reduce carbon dioxide in the dark. The dark reduction of carbon dioxide is very likely the first step in photosynthesis and can be represented by the equation $RH + CO_2 \rightleftarrows RCOOH$. Decarboxylation experiments have shown that the bulk of the radioactive carbon is in the carboxyl group. Attempts to identify the radioactive substances formed in the dark and in the light have been thus far unsuccessful. It is of considerable interest to note that formaldehyde, which has played a prominent rôle in many proposed mechanisms, was not formed from the radioactive carbon dioxide introduced. Experiments with the ultracentrifuge and diffusion methods indicate the average molecular weight of the radioactive molecules to be ~ 1000, which explains the failure to identify chemically these molecules with any small molecules.

Smith and Cowie (S41) have also studied the photosynthesis mechanism. They observed the reduction of carbon dioxide in the dark, confirming the results of Ruben, Kamen, and Hassid. They also used radioactive carbon dioxide to show that carbon dioxide reacts with the calcium carbonate, magnesium carbonate, etc. present in plants to form HCO_3^-.

Barker, Ruben, and Kamen (B43) have used radioactive carbon dioxide in a study of the methane bacteria. In the presence of various alcohols, acids, etc. these bacteria produce methane. The radiocarbon experiments have clearly shown that the methane arises from a complete reduction of carbon dioxide and not from a reduction of the organic substrate.

Similarly it was found by Carson and Ruben (C35) that carbon dioxide is reduced exclusively to two acids, propionic and succinic, by the propionic acid bacteria. They suggest that these results may be of general interest in connection with a major problem encountered in tracer experiments with labelled carbon,—namely, the synthesis of radioactive molecules starting with radioactive carbon dioxide. In many instances the appropriate microörganisms may offer the best method for the desired synthesis. For example, the propionic acid bacteria converted in 30 min. over 80 per cent of the radioactive carbon dioxide into propionic and succinic acids, which were thus made readily available with a very high specific activity for further tracer experiments.

Ruben and Kamen (R29) have found that a number of heterotrophic systems, previously thought only to produce carbon dioxide in their oxidation reactions, reduce carbon dioxide. In the case of yeast, for example, one carbon dioxide molecule is reduced for every fifty carbon dioxide molecules liberated in respiration. It would seem that carbon dioxide reduction is more widespread in living systems than has been hitherto suspected. This is of considerable interest, since it has been recently established that many microörganisms require small traces of carbon dioxide.

Mention should be made in this section of the experiments of Ruben, Hassid, and Kamen (R34), who have used radioactive N^{13} to show that barley plants fix small amounts of gaseous nitrogen, thus confirming the ideas of Lipman and Taylor (L49).

Hastings, Kistiakowsky, Cramer, Klemperer, Solomon, and Vennesland (H47) have made studies with lactic acid containing radioactive C^{11} in the carboxyl group. The purpose of the experiments, performed with rats, was to determine whether the increase of liver glycogen is or is not accompanied by radioactivity proportional to the amount of lactate converted to glycogen. The radioactivity of the glycogen, corresponding in weight to 33 per cent of the administered lactate, was only from < 1 to 3.6 per cent of that of the administered radioactive material. During the same time, the expired carbon dioxide contained more than 10 per cent of the radioactive carbon administered as lactate. They conclude that these results suggest either (*1*) that the lactate molecule may undergo a stage of decarboxylation before conversion to glycogen or (*2*) that the increase in liver glycogen may have arisen in these experiments from some precursor other than the radioactive lactate.

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THE CHEMISTRY OF VITAMIN E[1]

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CONTENTS

I. INTRODUCTION

In 1922 Evans and his collaborators at the University of California (24, 25, 26, 27, 28, 29, 30, 31, 32) described the results of a long series of experiments which indicated that there was required, in animal nutrition, a dietary constituent necessary for normal reproduction. Young rats, fed for a sufficiently long time on a diet of purified foods with addition of the necessary salts and all of the known vitamins, lost the ability to reproduce. Upon the addition of certain vegetable products to the diet, the reproductive ability was regained. It followed that there existed, in the added vegetable products, an unknown factor which was necessary for the normal reproductive ability of rats. First designated as factor-X, the substance was later recognized as a vitamin and given the letter E (27, 130). It has also been called the antisterility factor or the reproductive vitamin. Although other vitamins, especially vitamin A, appear to exert an influence on the reproductive ability, this loss is most characteristic of a lack of vitamin E. The existence of vitamin E was at first disputed by several workers, but as the studies progressed, it was shown that these workers had used diets not quite free from vitamin E, and soon there was general

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agreement that the factor actually existed. Almost simultaneously with Evans' publications, Sure (129, 130, 131) and Mattill and his collaborators (95, 96, 97) published the results of their experiments, which also indicated the existence of the antisterility factor. These results have since been duplicated in many other laboratories. It is unfortunate, however, that the terms "antisterility vitamin" and "reproductive vitamin" were ever applied to vitamin E, for in no case has the vitamin been found to bring about reproductive ability where formerly this did not exist at all; neither does a dose larger than the minimum necessary for normal litters bring about any increase in the size of the litters. The function of the vitamin, so far as reproductive ability alone is concerned, is merely one of aiding or allowing a normal action to occur.

Further investigation of vitamin E was intensively undertaken by Evans and his associates, particularly by Evans and Burr (31, 32, 33). Extended series of experiments, involving many thousands of experimental animals, were carried out (31, 32, 33). The results showed that wheat-germ oil was the richest source of vitamin E, but the vitamin was also found in considerable amounts in cottonseed oil (100), lettuce oil, rice-germ oil, and other seed-germ oils (31, 103). The vitamin remains in the unsaponifiable part of the lipoid fraction (31, 32, 91). By processes of partition between different solvents, a sterol-free concentrate was obtained which was active in single doses of 10 mg. (31, 32).

The characteristic symptoms of lack of vitamin E differ in the sexes (24). In the female rat (31, 32) normal conception occurs, but this is followed by "resorption sterility." There is the usual pregnancy increase in weight for about 10 days, then the weight decreases and becomes normal at about the twentieth day. No litter is cast. The litter has been resorbed, but the resorption has no effect upon the next oestrus cycle. If, now, a female known to be in this state of resorption sterility is again mated, conception occurs as before. A day or so later, the animal is given in the food the substance to be tested. If this is active, the pregnancy will be terminated by the birth of a litter of living young. The vitamin E activity is often expressed as milligrams of the substance, fed in a single dose, necessary to cure the sterility and to produce litters in 50 per cent of the animals used (1, 2, 3, 4, 5, 31, 32, 105).

In male animals, the characteristic symptoms of lack of the vitamin are associated with the germinal epithelia and the spermatozoa. These degenerate until all sexual power is lost. These changes can be arrested by vitamin E only in the early stages; once the degeneration in the male animal has progressed very far, administration of the vitamin is of no use. At one time, it was suggested that there might be two vitamin E factors, one essential for male animals and the other essential for females (51), but later work has failed to substantiate this.

Along with these changes in the reproductive organs go other, more obscure, degenerative changes elsewhere. Recently Shimotori, Emerson, and Evans (106) have reported cases of muscular dystrophy caused by lack of vitamin E, and there are growth effects (22, 104) clearly discernible, as well as a characteristic paralysis of the hind quarters (33). Other effects, especially connected with the hypophysis and with the occurrence and growth of tumors, have been reported, but there is not complete agreement, as yet, about the connection between these effects and vitamin E.

At the close of the second stage in the study of vitamin E, it was possible to obtain a concentrate from wheat-germ oil which showed activity in doses of 10 to 20 mg. These were yellow to red oils which were extremely difficult to concentrate further. By high-vacuum distillation, Olcott and Mattill (100, 101, 103) were able to obtain a fraction boiling at 200–250°C. under 0.05–0.1 mm. pressure, which was active in doses of 5 mg., but the vitamin was damaged in this process by the high temperature necessary for the distillation. Evans, Emerson, and Emerson (34), as well as Todd, Bergel, and Work (133), subjected the concentrates to partition between petroleum ether and methanol and obtained highly active preparations; Drummond and collaborators (20, 21) used chromatographic adsorption to achieve the same end. But none of these procedures yielded the vitamin in crystalline form. At each stage in these separations the various fractions were assayed biologically, and, also at this time, measurement of the ultraviolet absorption spectra of these concentrates was begun. It was found that a parallel existed between the activity and the height of an absorption band at 2940 Å. (13, 14, 20, 21, 41, 98, 100, 101, 103, 137), and this proved to be a reliable guide in following the process of concentration. The curves are given in figure 1 (137): A is the curve for natural α-tocopherol, with circles and squares representing two different preparations; B is the curve for synthetic *dl*-α-tocopherol; and C is the curve for *m*-xylotocopherol. In figure 2 are given, for comparison, the curves of three model substances related in structure to the tocopherols; the similarities, as well as the differences, of the chroman and coumaran types are apparent from these curves.

These vitamin E concentrates are readily soluble in all lipoid solvents, and only slightly soluble in water. They withstand a temperature of about 200°C. and are fairly stable in the air when in mass, although when finely divided they are attacked by air, and lose their activity. Ultraviolet light quickly destroys all of the activity (21). The concentrates are quite stable toward acids, much less so toward alkalis (31). They are resistant to reduction but are quickly attacked by oxidizing agents, even by such mild oxidizing agents as ferric chloride. Potassium permanganate, in pyridine solution, is rapidly reduced even in the cold (103). Ozone inactivates the vitamin (101). The presence of an active hydrogen atom was shown by the Zerewitinoff procedure (20). Acetyl chloride and benzoyl chloride react to produce esters (100, 101, 103), and these esters have practically the same activity as the original material. By comparing the shift in the maximum of the absorption spectrum that takes place when phenol is acetylated, with that occurring when vitamin E concentrates are acetylated, John, Dietzel, and Günther (63) were able to deduce that the hydroxyl group in vitamin E was phenolic in nature.

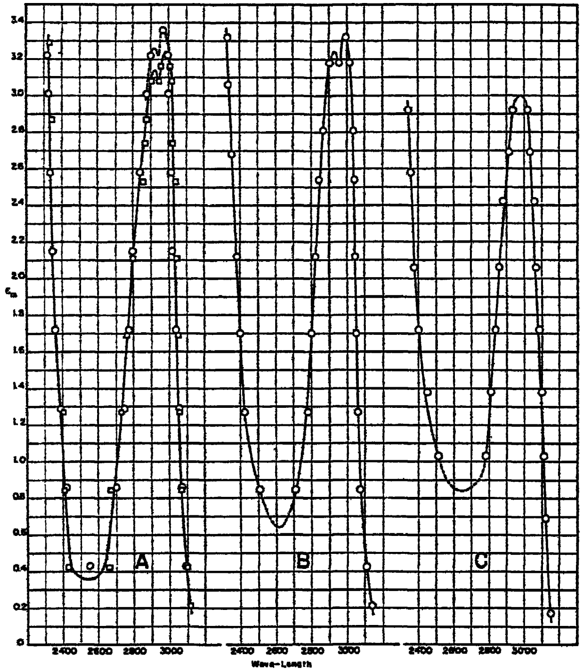
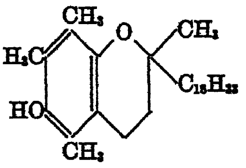
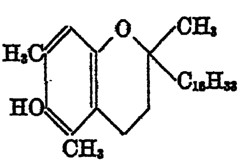


FIG. 1. Ultraviolet absorption spectra. A, curve for natural α-tocopherol; B, curve for synthetic *dl*-α-tocopherol; C, curve for *m*-xylotocopherol.



A and B



However, esterification of these concentrates by various acids failed to produce solid esters, and it was not until Evans, Emerson, and Emerson (34) treated the concentrates with cyanic acid that a solid derivative of

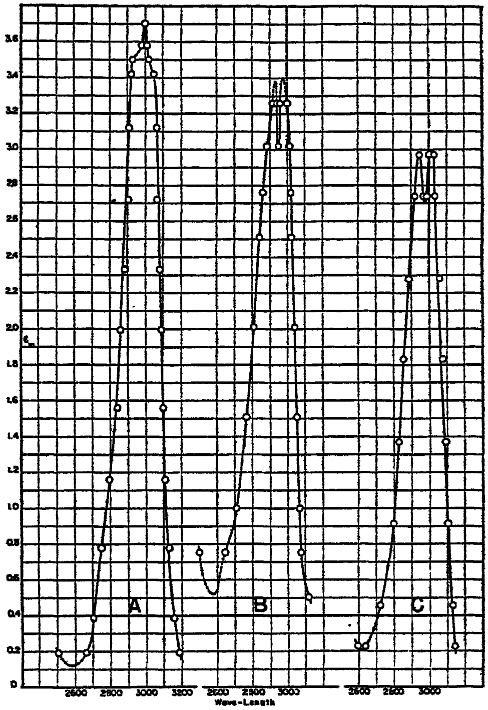
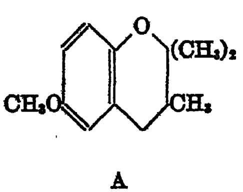
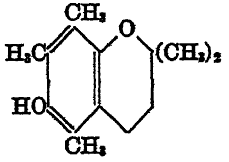


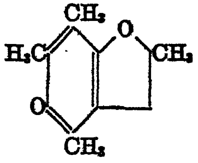
FIG. 2. Ultraviolet absorption spectra of three model substances related in structure to the tocopherols.



A



B



the vitamin was obtained. This reaction, characteristic of the hydroxyl group, leads to esters known as allophanates.

$$2HNCO + ROH \rightarrow H_2NCONHCOOR$$

By careful purification of the solid obtained in this way from wheat-germ oil concentrates there was obtained an allophanate melting at 159–160°C. and another melting at 138°C. These allophanates were soon isolated in other laboratories (20, 133); careful recrystallization of the allophanate melting at 138°C. gave a product which melted at 144–146°C. (41, 133). These allophanates were hydrolyzed, and each yielded a pale yellow oil. These oils were both highly active, the first in 3-mg. doses, the second in 8-mg. doses. For these individual vitamin E factors Evans coined the name tocopherol; the tocopherols were then designated as α- and β-tocopherols. From 1 kg. of wheat-germ oil, about 1 g. of α-tocopherol allophanate may be obtained, although the yield is often much less than this. α-Tocopherol was converted into the *p*-nitrophenylurethan, m.p. 129–131°C.; it was then recovered from this derivative by hydrolysis, and reconverted into the allophanate, which again melted at 158–160°C.

α-Tocopherol possesses all of the properties of the highly active concentrates from wheat-germ oil. It shows the same solubility behavior, and the absorption band at 2940 Å. is the same. Analysis shows the composition to be $C_{29}H_{50}O_2$. The homogeneity of the preparation was shown by converting it, as stated above, into a solid *p*-nitrophenylurethan (and a solid *p*-nitrobenzoate) and transformation of these into allophanates with the same melting point as that possessed by the original allophanate from the concentrates.

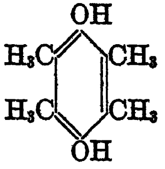
β-Tocopherol, obtained in the same way from its allophanate, is likewise an oil. Its properties are almost identical with those of α-tocopherol, but its composition is $C_{28}H_{48}O_2$ and so it is a lower homolog of α-tocopherol. The yield of β-tocopherol from wheat-germ oil is usually much smaller than the yield of α-tocopherol, but often, from oils of different sources, normal amounts of β-tocopherol can be isolated, while almost no α-tocopherol can be found.

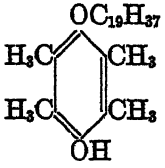
A third allophanate, melting at 138–140°C., has been isolated from cottonseed oil by Emerson, Evans, and their associates (41). This has been named γ-tocopherol allophanate. γ-Tocopherol is likewise an oil, active in 8-mg. doses, and it is an isomer of β-tocopherol, having the composition $C_{28}H_{48}O_2$.

We have, then, three antisterility factors which are responsible for vitamin E activity. These three tocopherols appear to be the only substances isolated from natural material which certainly possess vitamin E activity, for reports of still other active principles have not been substantiated (57, 80, 88, 89).

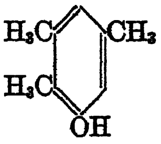
II. α-TOCOPHEROL

As mentioned above, α-tocopherol possesses the composition $C_{29}H_{50}O_2$. This composition is very close to that of some of the sterols,—sitosterol, for instance, having the composition $C_{29}H_{50}O$. As dehydrogenation with selenium had been of such great value in connection with studies of structure in the field of the sterols, it was natural that this method should be applied to α-tocopherol. McArthur and Watson (92) heated α-tocopherol with selenium; the result was a yellow sublimate, duroquinone, and a red oil. Somewhat later Fernholz (44) pyrolyzed α-tocopherol at 350°C. in the absence of any dehydrogenating agent. There was obtained a good yield of a white crystalline sublimate, identified as durohydroquinone (I), together with a red oil. Similarly, β-tocopherol gave trimethylhydroquinone (10, 55). The simplest assumption which would account for these decomposition products was that α-tocopherol was a monoether of hydroduroquinone (44, 55), such as II (in which the group $C_{19}H_{37}$ contained one saturated ring), for it was known that many alkyl ethers of phenols were cleaved by pyrolysis into the phenol and an unsaturated hydrocarbon. Accordingly, in several laboratories monoethers of hydroduroquinone and of other hydroquinones were synthesized. Some of these showed activity when assayed biologically, but these ethers differed markedly from α-tocopherol in chemical properties and their ultraviolet absorption spectra were also quite different from that of the vitamin. As a result of these studies, it quickly became apparent that α-tocopherol could not be a simple monoether of hydroduroquinone (11, 58, 89, 99). John, Dietzel, and Günther (63) had also obtained pseudocumenol-6 (isopseudocumenol), III, by heating α-tocopherol with hydriodic acid; this result was also difficult to reconcile with the assumption that α-tocopherol was a simple monoether of hydroduroquinone, but it could be reconciled with the assumption that a second ring was condensed with the aromatic nucleus, probably involving an oxygen atom. Bergel, Todd, and Work (11) found that α-tocopherol, when energetically hydrogenated, absorbed 4 moles of hydrogen and they, too, supposed that an oxide ring was a part of the structure of the vitamin.



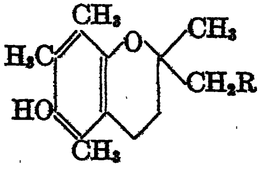


II



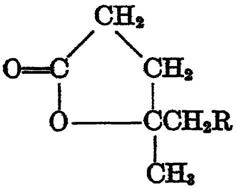
III

The correct structure for α-tocopherol (IV) was proposed by Fernholz (45) as a result of oxidative degradation, using chromic acid as the oxidizing

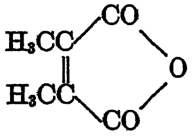


IV

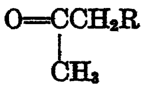
agent. The products were a C_{21} lactone (V), dimethylmaleic anhydride (VI), a C_{18} ketone (VII), a C_{16} acid (VIII), together with diacetyl and acetone.



V



VI



$\begin{array}{l}O{=}CCH_2R\\ \;\;|\\ \;\;CH_3\end{array}$

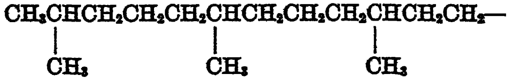
VII

HOOCR

VIII

$CH_3COCOCH_3$ CH_3COCH_3

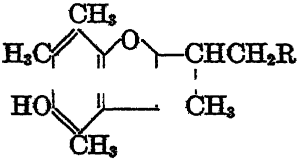
R = $C_{15}H_{31}$— or



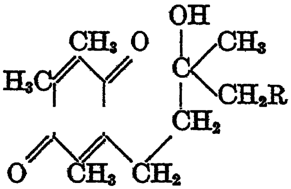
$CH_3\underset{\underset{\displaystyle CH_3}{|}}{CH}CH_2CH_2CH_2\underset{\underset{\displaystyle CH_3}{|}}{CH}CH_2CH_2CH_2\underset{\underset{\displaystyle CH_3}{|}}{CH}CH_2CH_2—$

The hydroxy acid corresponding to the lactone V was transformed into the lactone with extreme ease, indicating that it was a γ-hydroxy acid; moreover, the hydroxyl group of the acid could not be oxidized to a carbonyl group, and was esterified only with difficulty. These facts indicated that the hydroxyl group was tertiary. The C_{16} acid (VIII), when analyzed for C—CH_3 groups, showed three such groups. The structure for the lactone (V) can only be written as shown in order to explain the formation from it of a C_{18} ketone and a C_{16} acid, and when these degradation products are assembled, they lead unequivocally to the structure IV, that of a chroman, for α-tocopherol. These results do not, of course, lead to the structure shown for the group R, $C_{15}H_{31}$. The structure for this group was written on the basis of the C-methyl determination and the experiences gained in other fields of natural products which frequently contain chains of "isoprene" units joined head to tail.

Karrer (80, 89), although considering both the chroman (IV) and the coumaran (IX) structures for α-tocopherol, at first preferred the latter. However, John and his associates (58) showed that α-tocopherol, when



IX



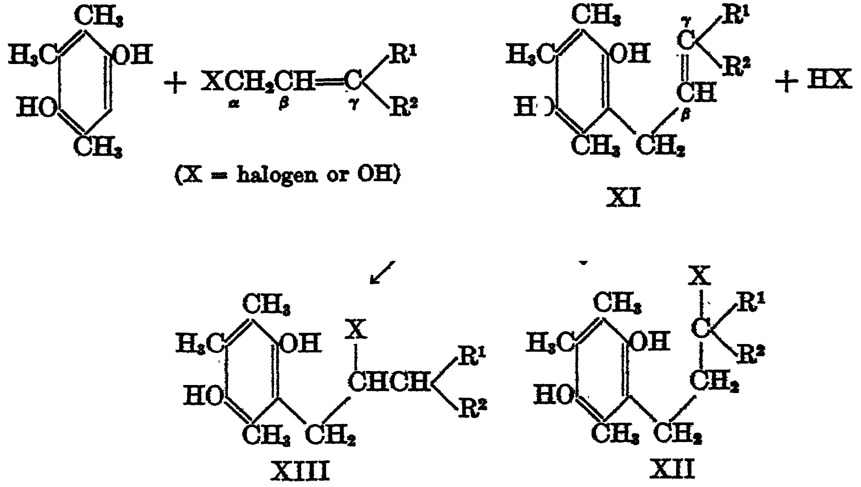
X

R = $C_{15}H_{31}$—, as in structure IV

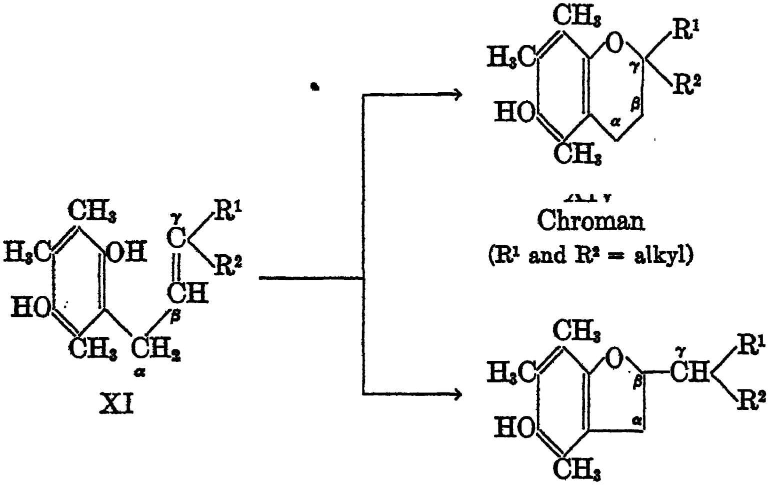
oxidized carefully with silver nitrate or ferric chloride, gave a yellow quinone (X). This quinone could be reduced to a hydroquinone, the di-*p*-bromobenzoate of which was quite stable toward chromic oxide, a fact which indicated that the hydroxyl group in X was tertiary. This could only be true if the oxygen ring in α-tocopherol were a chroman, for the coumaran IX would on oxidation give a hydroxyquinone, the hydroxyl group of which would be secondary and so susceptible to ready oxidation by chromic oxide. Karrer based his selection of the coumaran formula (IX) upon the fact that allyl bromide, when condensed with trimethylhydroquinone, does give a coumaran, and when he synthesized α-tocopherol from phytyl bromide, trimethylhydroquinone, and zinc chloride (79) he stated that structure IX was "highly probable."

The synthesis of chromans such as IV is often, but by no means always, rather simple and easy. The starting materials are hydroquinones (or phenols) having vacant one position in the ring ortho to the hydroxyl group (42, 81, 116). These are condensed with allylic halides or alcohols, or with conjugated dienes (7, 8, 79, 80, 119, 126). Frequently the reaction proceeds so smoothly that neither solvent nor catalyst is required, especially when allylic bromides or chlorides are used. When the alcohols or the dienes are used, it is customary to employ both a catalyst and a solvent. But in any event, because of the great reactivity of the allylic compounds, coupled with the enhanced activity of the aromatic nucleus in polyalkyl benzene derivatives, reactions between the two classes of compounds take place readily and the products are often obtained in good yields.

Using the halides or the alcohols, the first step in the reaction appears to be a direct introduction of the allyl group (121, 128) without rearrangement, to give XI.



Frequently, when X is halogen, the HX addition products (XII or XIII) of the allylic compounds (XI) can be isolated. The second step in the reaction, the ring closure, involves the addition of the hydroxyl group to the double bond in the side chain of XI, in accordance with Markownikoff's rule.



XI

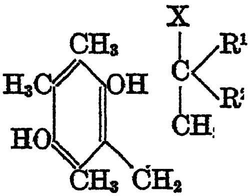
XIV
Chroman
(R¹ and R² = alkyl)

XV
Coumaran
(R¹ and R² = hydrogen)

Hence, whether a chroman or a coumaran will be formed in this reaction will depend upon the nature of the groups or atoms attached to the γ-carbon atom in the allylic compound. If these groups are both alkyl, the oxygen of the hydroxyl group will add to the γ-carbon atom and the product will be a chroman (XIV); while if these groups are both hydrogen, addition will occur in the reverse manner and the product will be a coumaran (XV). When one of the groups is alkyl and the other is hydrogen, the product might be either the chroman or the coumaran, or a mixture of the two, although in most of these cases which have been studied so far it is largely the chroman. In a recent paper, Karrer, Escher, and Rentschler (74) have made similar generalizations about these ring closures; they have isolated, as condensation products of trimethylhydroquinone and crotyl bromide, *both* the chroman (XXXIII) and the coumaran (XXXIIIa). The structure of the latter was proved by an independent synthesis, using the sequence of reactions shown for the synthesis of XVI, substituting propionylacetic ester for acetoacetic ester.

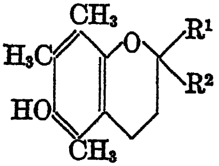
However, it is very curious in this connection that condensation of trimethylhydroquinone with either crotyl *chloride* or butadiene (111) gave the same product, melting at 145°C. Mixtures of these two products did not show any depression in melting point, and according to previous work (74) this product was 2,5,7,8-tetramethyl-6-hydroxychroman (XXXIII; page 22). The isomeric 2-ethyl-4,6,7-trimethyl-5-hydroxycoumaran (XXXIIIa), isolated along with the chroman from the condensation product of crotyl *bromide* and trimethylhydroquinone (74), was reported to melt at 120°C. alone or when mixed with the chroman XXXIII, m.p. 145°C. Yet the series of reactions involving compounds LII, LV, LVI, LVII, and XXXIII has been reported (66). The last step, from LVII to XXXIII, involved the action of hydrobromic acid upon a solution of the ketone LVII in acetic acid, whereby the methoxyl groups were cleaved, and, simultaneously, reduction and ring closure occurred. The chroman XXXIII, made in this way, was reported to melt at 145°C. This experiment was repeated, *via* LII, LIII, LIV, and LVII (111), but the product, although it melted at 143°C., was *not* identical with XXXIII prepared from trimethylhydroquinone and crotyl chloride, crotyl bromide, or butadiene. A mixture of the two substances (both melting at 143–145°C.) melted at 115–130°C. Moreover, the product prepared from the ketone LVII gave a red color immediately with alcoholic silver nitrate, while the product prepared by condensation of trimethylhydroquinone and crotyl chloride or butadiene gave only a yellow oil with alcoholic silver nitrate. This yellow oil, when reductively acetylated, gave a monoacetate which melted at 79–80.5°C. and which was identical with the monoacetate (m.p. 84–85°C.) obtained from the condensation product itself (111). It then appears that the ketone LVII can be converted into the same product as that obtained by condensation of trimethylhydroquinone with crotyl bromide, but this product is certainly different from the substance obtained by condensation of the hydroquinone with either crotyl chloride or butadiene.

The halogen-containing products, XII and XIII, follow the same general rules. These can be readily cyclized to ring compounds, HX being eliminated between the halogen atom and the hydrogen atom of the hydroxyl group. It is to be noted that Markownikoff's rule also plays a part in these reactions, for although XII cyclizes to XIV (R^1 and R^2 are alkyl), the addition of HX to the double bond in XI could occur in two ways and the mode of addition will be governed by the rule. Thus when R^1 and R^2 in XI are alkyl groups, HX will add so as to produce XII; but when R^1 and R^2 are hydrogen atoms, HX will add so as to produce XIII. The ensuing ring closure by elimination of HX would then give the chroman XIV from XII and the coumaran XV from XIII.

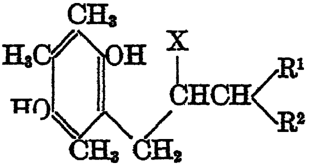


XII

HX +

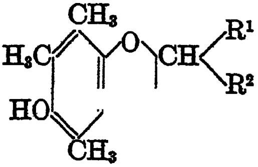


XIV



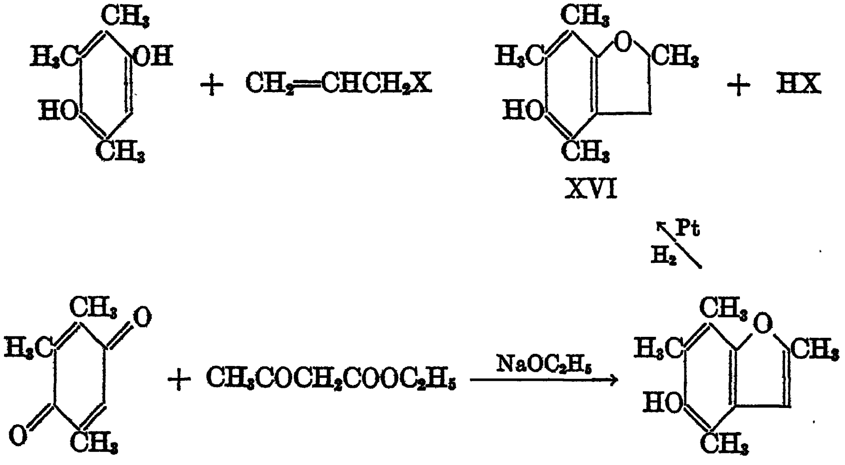
XIII

HX +



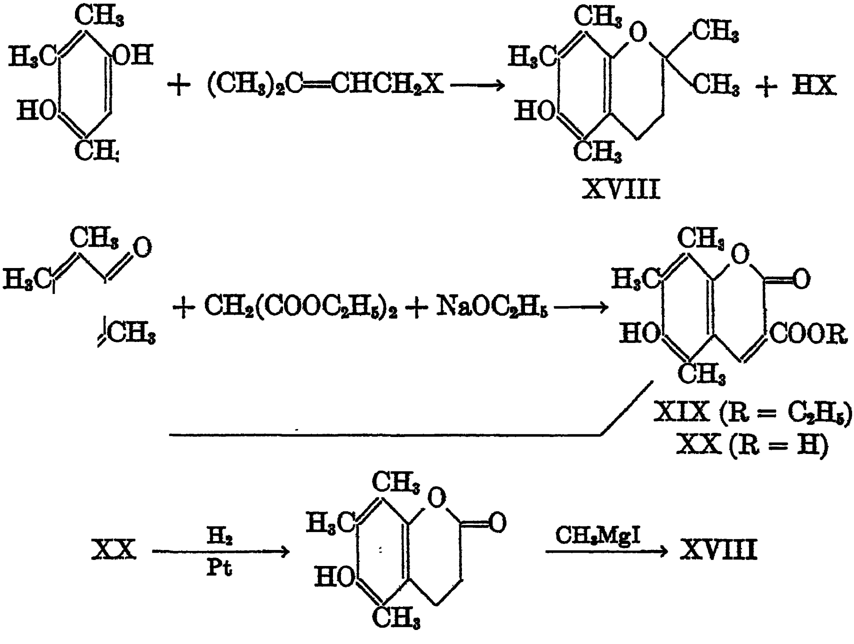
XV

The generalities stated above regarding these reactions were carefully checked by means of model experiments upon simple compounds, the structures of which could be proved by independent syntheses. Thus, when allyl bromide or chloride is condensed with trimethylhydroquinone, the product is the coumaran XVI (121, 126), which is also produced by reduction of the coumarone XVII whose structure had previously been proved (115).



XVII

When γ,γ-dimethylallyl bromide is used, the ring closure occurs in the reverse direction and a chroman (XVIII) is produced (121, 126, 127). The structure of this chroman also was proved by an independent synthesis from coumarin derivatives (XIX, XX, and XXI) of known structure (109, 110).


XVIII

XIX ($R = C_2H_5$)

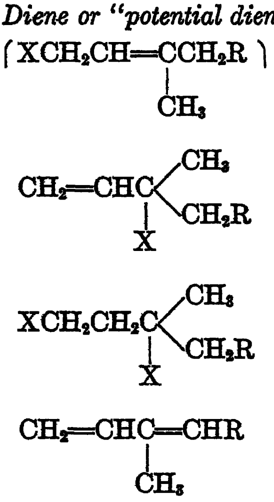
XX ($R = H$)

XXI

This same chroman (XVIII) has also been synthesized in other ways (66, 68, 125), so that there can be no doubt as to its structure; it is also the product of the reaction between trimethylhydroquinone and isoprene (122, 126, 128), a fact which has an important bearing upon the mechanism of these condensations (128).

In all this work involving condensations of hydroquinones with allylic compounds and with dienes, Markownikoff's rule has been assumed to apply fully, since the nature of one of the reactants (hydroquinones) insured that the reaction occurred under antioxidant conditions. Any "peroxide effect" therefore was considered to be negligible. Recently, however, it has been shown that the antioxidant effect of allylic phenols could be avoided by conversion of the phenols into acetates, and under these conditions there was a definite "peroxide effect" when the allylic phenol acetates were cyclized (52). Thus, when *o*-allylphenol was cyclized, the product was 2-methylcoumaran under all conditions. However, the *acetate* of this phenol, subjected to the action of hydrobromic acid, gave *2-methylcoumaran* when hydroquinone was present, and *chroman* when ascaridole (or other peroxides) was present. In a similar fashion, the acetate of *o*-allyl-*p*-cresol was converted into 2,5-dimethylcoumaran when hydroquinone was present, and into 6-methylchroman when peroxides were present. Other allylic phenols were found to be susceptible to this directed ring closure: these included *o*-allyl-*o*-cresol, *o*-allyl-*p*-bromophenol, and *o*-crotylphenol. But in the case of the one γ,γ-disubstituted allylic phenol studied, namely *o*-(γ,γ-dimethylallyl)phenol, the tendency toward chroman formation was so great that the product from the acetate was 2,2-dimethylchroman regardless of whether hydroquinone or benzoyl peroxide was present (52).

As stated above, conjugated dienes can be condensed with phenols and hydroquinones to give chromans and coumarans, and it is a fact that allylic carbinols, halides, and conjugated dienes, as well as appropriate diols and dihalides which give conjugated dienes when treated with catalysts, all condense with phenols to give chromans and coumarans (16, 128). These reactions have recently been extended to methylated hydroquinones (122, 126, 128) and in particular to the synthesis of tocopherols (7, 8, 79, 119, 126, 128). Claisen (16), who carried out the early work upon the phenols, implied that in all of these condensations the conjugated diene was an intermediate regardless of the halogen or hydroxyl compound used.


Diene or "potential diene"

$\left\{XCH_2CH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}CH_2R\right\}$

Hydroquinones or phenols } condensed with

$CH_2{=}CH\underset{\displaystyle X}{\underset{|}{C}}\begin{matrix}\diagup CH_3\\ \diagdown CH_2R\end{matrix}$

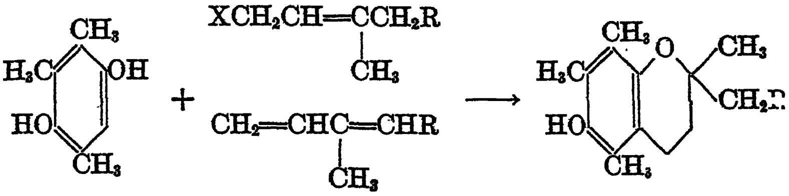
$XCH_2CH_2\underset{\displaystyle X}{\underset{|}{C}}\begin{matrix}\diagup CH_3\\ \diagdown CH_2R\end{matrix}$

$CH_2{=}CH\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CHR$

give chromans and coumarans, *via* the conjugated diene

X = OH or halogen; R alkyl

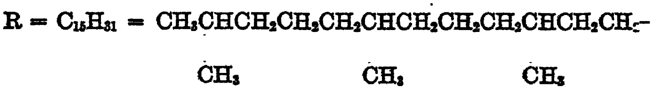
When it was found that phytadiene could be condensed with trimethylhydroquinone to produce α-tocopherol (122, 126), Claisen's mechanism appeared to offer a common explanation of the formation of tocopherols from hydroquinones and phytyl halides (7, 8, 75, 79, 119, 126), phytol (126, 128), and phytadiene (122, 126, 128).



IV

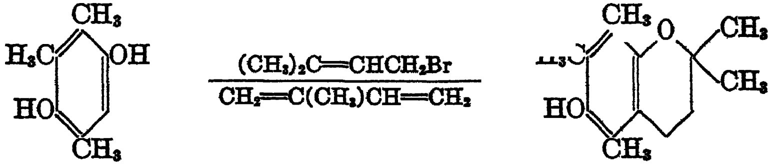
X = OH or halogen

α-Tocopherol

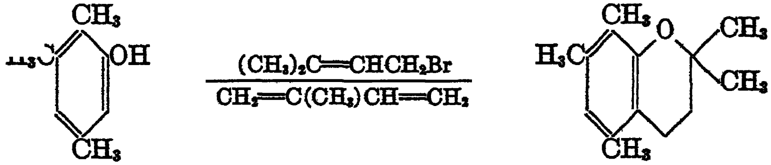


$R = C_{15}H_{31} = CH_3\underset{CH_3}{C}HCH_2CH_2CH_2\underset{CH_3}{C}HCH_2CH_2CH_2\underset{CH_3}{C}HCH_2CH_2-$

In harmony with this conception is the formation of the chromans XVIII and XXII when either γ,γ-dimethylallyl bromide or isoprene is used (121, 122). But this mechanism

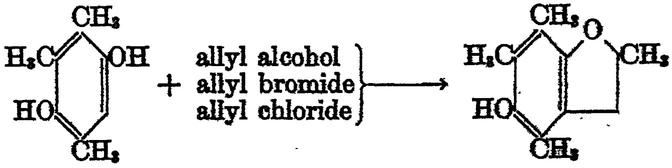


XVIII



XXII

offers some difficulties when considered in the light of known facts regarding the addition of phenols to double bonds. In the first place, allyl alcohol, allyl bromide, and allyl chloride all condense with 2,3,5-trimethylhydroquinone to give the coumaran XVI and it is obvious that the corresponding diene (allene, $CH_2=C=CH_2$) cannot be an intermediate in this case unless an unusual mode of addition of the hydroquinone is postulated. Secondly, in some of the reactions between conjugated dienes and phenols,



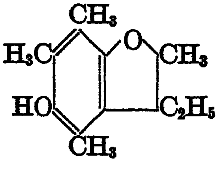
XVI

hydroquinones, and their derivatives, allylic phenols or their HX addition products (XI, XII, XIII) are formed (122), and these may be cyclized in a separate operation, giving rise to the same cyclic compound whether the reaction is carried out in one step or in two. With a substituted diene such as isoprene, therefore, it is again difficult to interpret the reaction as a direct addition of the phenol or hydroquinone to the diene without assuming an unusual mode of addition, since the intermediate is known to contain a γ,γ-dimethylallyl group.

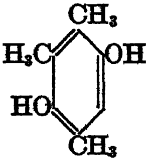
In order to reach a decision as to whether or not the diene is an intermediate, ethylvinylcarbinol (XXIII) and 1,3-pentadiene (XXIV) were condensed with trimethylhydroquinone under identical conditions (128). Since the diene to be expected from XXIII is XXIV, these two substances should give the same products when condensed with the hydroquinone, providing that the diene is an intermediate. Actually, however, the two products are different; the carbinol gave the coumaran XXV, while the diene gave the chroman XXVI.

$CH_3CH_2CHOHCH{=}CH_2$

XXIII

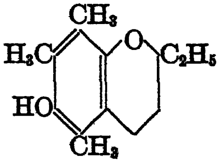


XXV



$CH_3CH{=}CHCH{=}CH_2$

XXIV



XXVI

Thus the diene cannot be an intermediate in the formation of XXV, and some other mechanism must be devised to account for the known products obtained in these condensations. A tentative hypothesis, which accounts for all of the known facts, is as follows: the *alcohols* and *halides*, as stated above, react with the phenol or hydroquinone by direct nuclear "allylation" without rearrangement; ring closure then follows in accordance with Markownikoff's rule. The *dienes* react first by 1,4-addition of the acidic catalyst (proton); this intermediate then "allylates" the aromatic nucleus without rearrangement, and ring closure follows as before. Hence 1,3-pentadiene (XXIV), isoprene, 2,3-dimethylbutadiene, phytadiene (XXIX), and other similarly constituted dienes with terminal CH_2 groups (XXVII; R^1, R^2, R^3 = hydrogen or alkyl) all give the same products as would be obtained using the halide or alcohol XXVIII (R^1, R^2, R^3 =

hydrogen or alkyl; X = hydroxyl or halogen). On the other hand, the secondary and probably also the tertiary allylic alcohols and halides give products different from those obtained from the diene, and this regardless of whether the alcohols and halides are single substances or mixtures of allylic isomers, so long as one of the allylic isomers is not related to the diene as XXVIII is to XXVII. Thus methylvinylcarbinol and hydroquinone give the chroman XXXII *via* the intermediate XXX, while crotyl bromide gives the chroman XXXIII (74, 128) and the coumaran XXXIIIa (74) *via* the intermediate XXXI.

$R^1CH{=}C(R^2)CR^3{=}CH_2$ (XXVII)

$CH_3CH{=}CHCH{=}CH_2$ (XXIV)

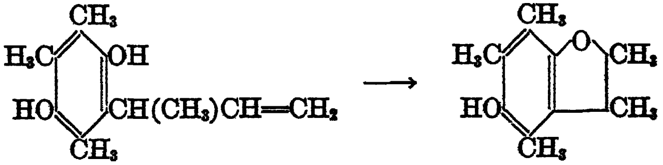
$CH_2{=}C(CH_3)CH{=}CH_2$

$CH_2{=}C(CH_3)C(CH_3){=}CH_2$

$C_{15}H_{31}CH{=}C(CH_3)CH{=}CH_2$ (XXIX)

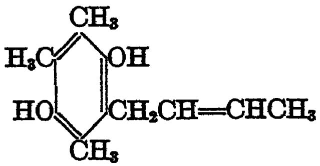
All dienes with terminal CH_2 group

$R^1CH_2C(R^2){=}C(R^3)CH_2X$ (XXVIII)

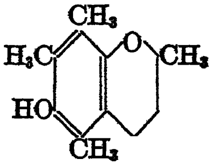


XXX
(Intermediate using methylvinylcarbinol)

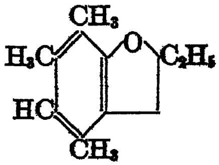
XXXII



XXXI
(Intermediate using crotyl bromide)



XXXIII
(largely)

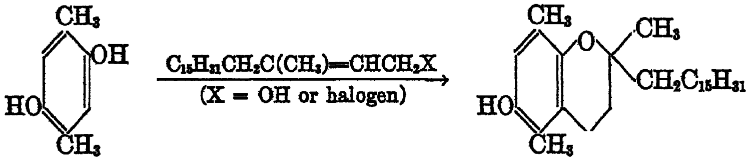


XXXIIIa
(by-product)

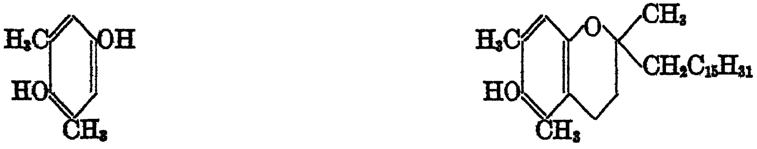
Using this reaction scheme, it can be readily understood that phytol, phytyl halides, and phytadiene should all condense with trimethylhydroquinone to give α-tocopherol, a prediction in complete accord with the facts. Thus it is possible to use a variety of starting materials and so to synthesize in several ways compounds containing the chroman or coumaran ring. These reactions all take place readily, and the syntheses of α-tocopherol described here involve no laborious syntheses of complicated intermediates, as is so often the case in vitamin syntheses.

III. β-TOCOPHEROL

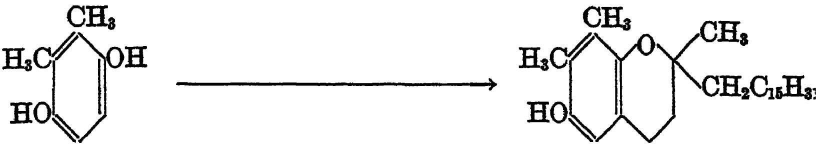
As stated before, β-tocopherol possesses the composition $C_{28}H_{48}O_2$ and is a lower homolog of α-tocopherol. On thermal decomposition, it gives a sublimate of trimethylhydroquinone (11, 55); cleavage with hydriodic acid leads to *p*-xylenol (63). These reactions indicate that β-tocopherol possesses one less methyl group in the aromatic nucleus than does α-tocopherol, and the proof that this is the only difference between β- and α-tocopherol was supplied by Emerson (39) who, using the procedure of Fernholz, obtained from β-tocopherol practically the same degradation products as had been obtained from α-tocopherol. All of these facts indicated that the two methyl groups in the aromatic ring of β-tocopherol were para to each other and that this tocopherol was a derivative of *p*-xylohydroquinone with the structure XXXIV. This structure was proved by the synthesis of β-tocopherol; in fact, all three of the "xylotocopherols" have been synthesized (7, 8, 54, 75, 76, 78, 79, 80, 86, 119).



XXXIV
"*p*-Xylotocopherol"
(β-Tocopherol)

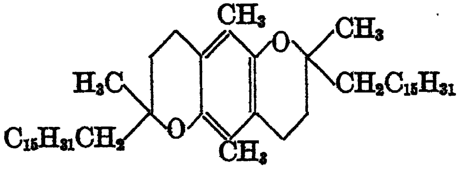


XXXV
"*m*-Xylotocopherol"

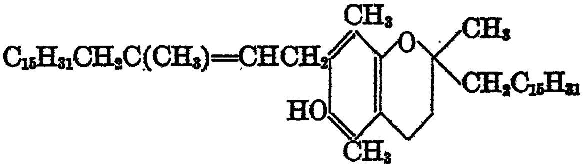


XXXVI
"*o*-Xylotocopherol"
(γ-Tocopherol)

These syntheses, however, proved to be much more difficult than the synthesis of α-tocopherol. The great reactivity of the allylic alcohol or halide (phytol or phytyl bromide) used, coupled with the enhanced reactivity of the aromatic nucleus due to the presence of the methyl groups, led to the easy introduction of more than one phytyl group, resulting in the formation of complicated mixtures from which the separation of the tocopherols was extremely tedious and difficult. These by-products were substances of the type of XXXVII, XXXVIII, XXXIX, XL, and XLI.

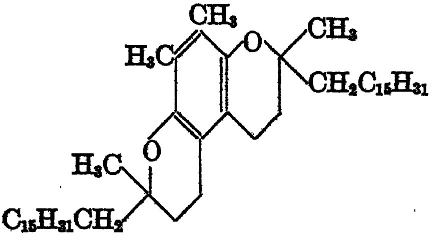


XXXVII

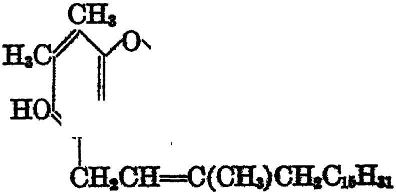


XXXVIII

By-products in the synthesis of *p*-xylo(β)tocopherol

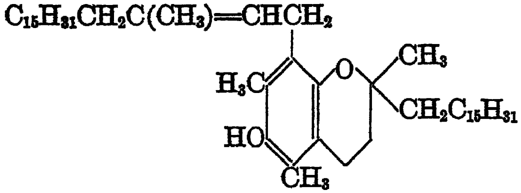


XXXIX



XL

By-products in the synthesis of *o*-xylo(γ)tocopherol



XLI

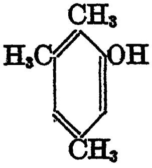
By-product in the synthesis of *m*-xylotocopherol

The allophanates of the xylotocopherols do not crystallize well from these mixtures, but by repeated chromatographic adsorption combined with crystallization of the allophanates, Karrer (76) was able to isolate the allophanate and the *p*-nitrophenylurethan of *m*-xylotocopherol (XXXV), which melted at 150° and 90°C., respectively, as well as the allophanate and the *p*-nitrophenylurethan of *p*-xylotocopherol (XXXIV), which melted at 154–155° and 91°C., respectively. The allophanate of *o*-xylotocopherol (XXXVI) was also isolated (78); it melted at 146°C. These derivatives of *p*-xylotocopherol (XXXIV) showed no depression in melting point when mixed with the corresponding derivatives of natural β-tocopherol (m.p. 146° and 90°C., respectively). This synthesis therefore completed the proof that β-tocopherol is *p*-xylotocopherol (XXXIV). The English group, however, report the melting point of the *p*-nitrophenylurethan of *p*-xylotocopherol as 111–112°C. (Karrer (86) later checked this and also reported 111–112°C.), and that of *o*-xylotocopherol as 89°C. (54). All three of the xylotocopherols are biologically active when fed at 5- to 10-mg. levels (54, 75, 76, 119). Recent work (86) indicates that the xylotocopherols are somewhat more active biologically than was at first supposed. All three are 100 per cent active in 10-mg. doses; *o*- and *m*-xylotocopherols are about 50 per cent active in 5-mg. doses, although *p*-xylo(β)tocopherol, curiously enough, is inactive at this level. The para- and ortho-compounds are inactive in 2.5-mg. doses; data on the meta-compound were not reported at levels below 5 mg.

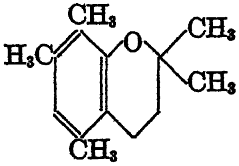
IV. γ-TOCOPHEROL

This tocopherol is also a lower homolog of α-tocopherol (39, 54). It is isomeric with β-tocopherol, and it has the composition $C_{28}H_{48}O_2$. On oxidation, γ-tocopherol gives many of the same products as were obtained from α- and β-tocopherols (39), particularly dimethylmaleic anhydride (38) (8 per cent yield as compared with 24 per cent yield from α-tocopherol (19)); it also yields trimethylhydroquinone on pyrolysis (39). These data indicate strongly that γ-tocopherol is *o*-xylotocopherol. The allophanate of γ-tocopherol melts at 137–140°C. γ-Tocopherol is extremely difficult to isolate and purify, because the allophanate of α-tocopherol is very similar to that of γ-tocopherol and mixtures of the two show depressions of only a few degrees in melting point. It has recently been found, however, that corn-embryo oil is relatively rich in γ-tocopherol and contains very little α-tocopherol, so that the isolation of the allophanate of γ-tocopherol from this source is much simplified (40). With larger amounts of γ-tocopherol available, the structure of this substance will doubtless be definitely settled soon.

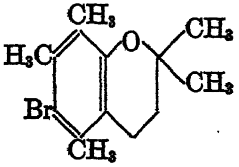
Because the synthesis of simpler tocopherols is accompanied by so many side reactions and by-products, attempts have been made to devise syntheses which avoid these complications (77, 112, 113, 117, 124). Since phenols are much less troublesome than hydroquinones as far as these by-products are concerned, the heterocyclic ring was built onto the phenol and the *p*-hydroxyl group then introduced as the final step in the synthesis (113). Thus 2,3,5-trimethylphenol (III) was condensed with isoprene to give the chroman XXII.



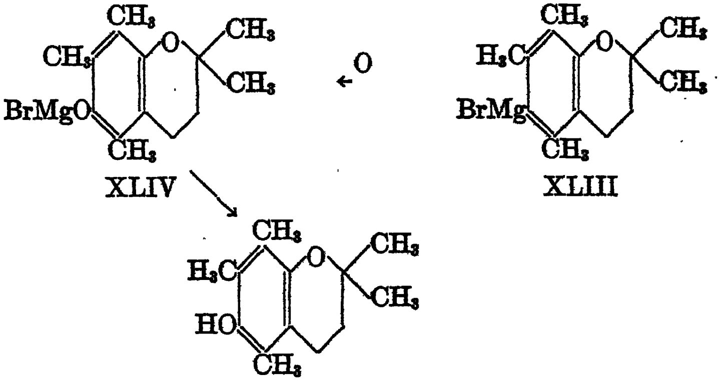
III



XXII

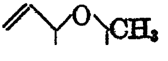


XLII

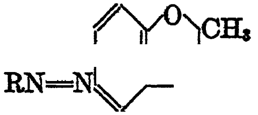


XVIII

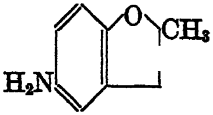
This was converted to the monobromo derivative (XLII), which reacted with metallic magnesium to produce the Grignard reagent XLIII. Oxidation of the magnesium derivative, followed by hydrolysis, produced the hydroxychroman XVIII, identical with that synthesized by other methods. No by-products were produced in these syntheses, but the over-all yield of XVIII left much to be desired. Experiments were also carried out in which chromans and coumarans were coupled with aromatic diazonium compounds (77, 113). Thus Karrer (77), by coupling the coumaran XLV with diazotized 2,4-dinitroaniline, prepared the azo compound XLVI, which was reductively cleaved to the aminocoumaran XLVII. The amino group of this coumaran was then diazotized and replaced by the hydroxyl group in the usual way, yielding the hydroxycoumaran XLVIII. The aminocoumaran XLIX was prepared in a similar manner.



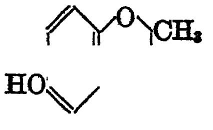
XLV



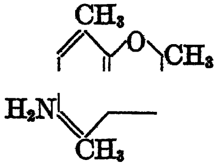
XLVI



XLVII

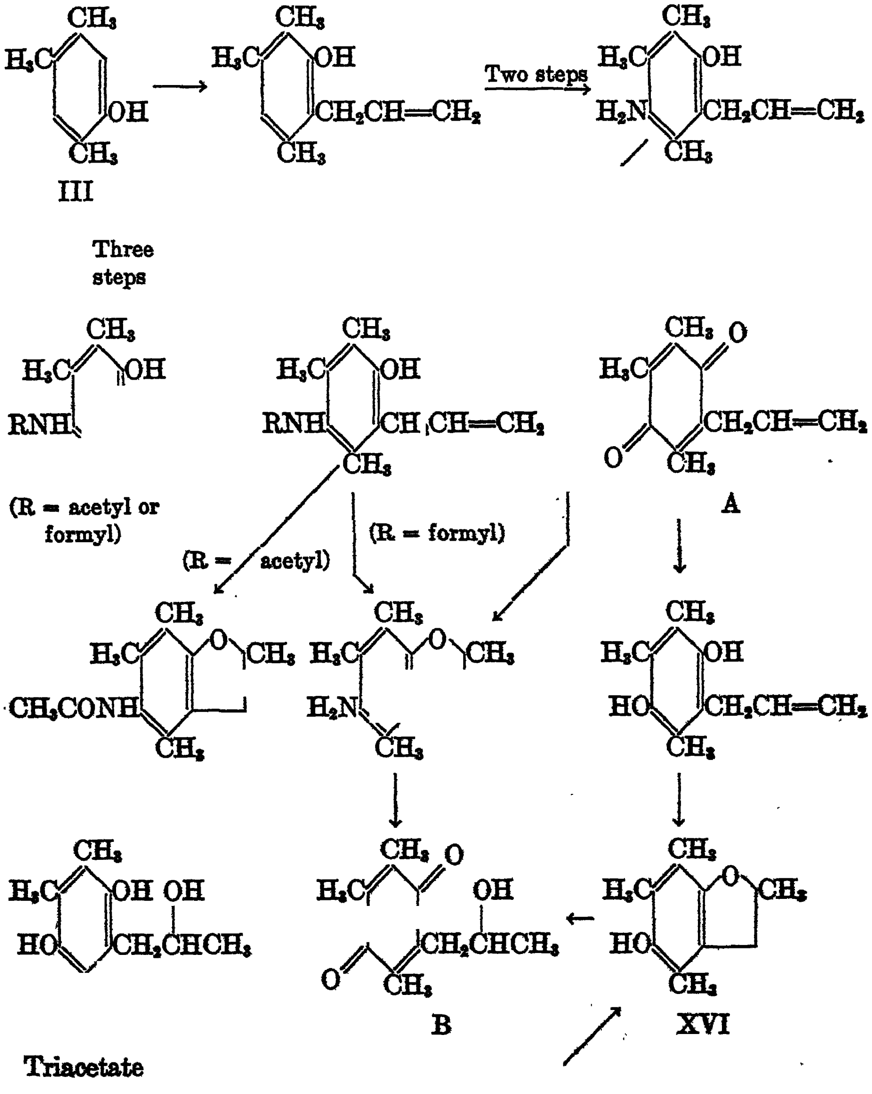


XLVIII

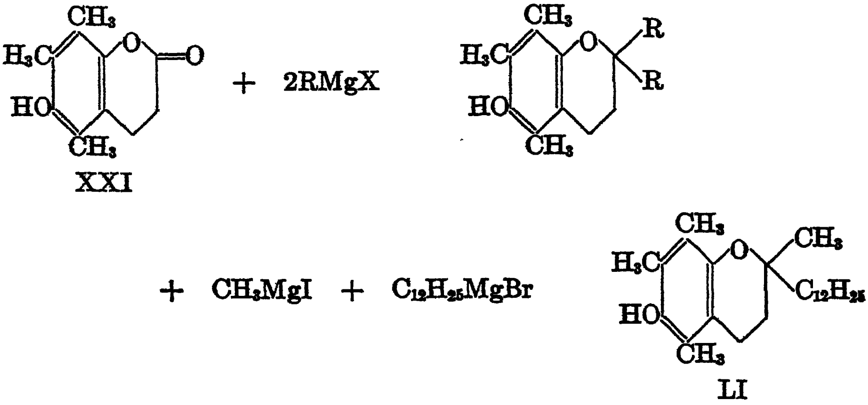


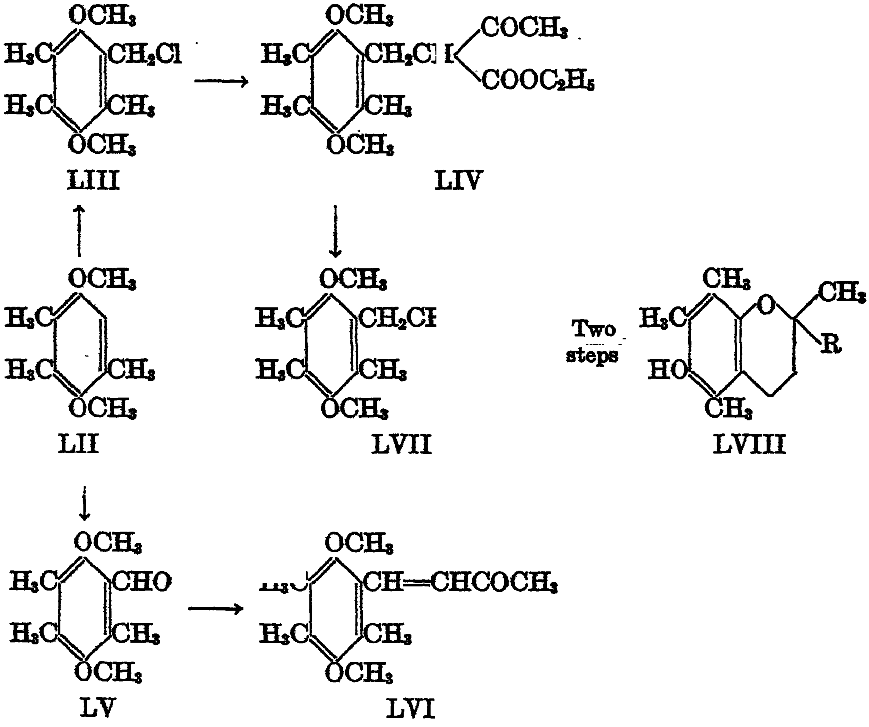
XLIX

In another such series (112), 2,3,5-trimethylphenol (III) was converted into 2,4,6,7-tetramethyl-5-hydroxycoumaran (XVI) by two routes, as shown below. All of the reactions leading to the coumaran proceeded smoothly and gave good yields, and whether the allyl group was introduced before or after the coupling made no difference. The use of diazotized sulfanilic acid in the coupling reactions was advantageous, because after cleavage the by-product (sulfanilic acid) was water-soluble and nonvolatile. This series of reactions, in which ring closure occurs *after* the coupling, is of especial value, since chromans and coumarans, being essentially phenol ethers, often do not couple well even with very active diazonium salts. The only step in the whole series of reactions which gave rise to any difficulty was the cleavage of the acetaminocoumaran to the aminocoumaran; this cleavage could not be achieved by any of the methods tried. But the formylamino compounds offered no difficulty at any step; treatment of trimethylallylformaminophenol with hydrobromic acid gave the aminocoumaran hydrobromide in good yield. The hydroxycoumaran XVI was prepared equally well *via* the two quinones A and B, one of which (A) contained the unsaturated allylic side chain, while the other (B) contained the saturated, but hydroxylated, side chain. Many alternative paths from III to XVI involving the compounds in the chart naturally suggest themselves; while all of these were not tried, there was no evidence that the introduction of the various groups, as well as the ring closure, could not have been done in any desired order. An analogous series of reactions was also used for preparing 2-methyl-5-hydroxycoumaran. *o*-Allylphenol was converted, *via* the azo compound, into *o*-allyl-*p*-aminophenol, which was then oxidized to allylquinone. The quinone was reduced to the hydroquinone and the latter cyclized to the coumaran. The over-all yield of 2-methyl-5-hydroxycoumaran was excellent.



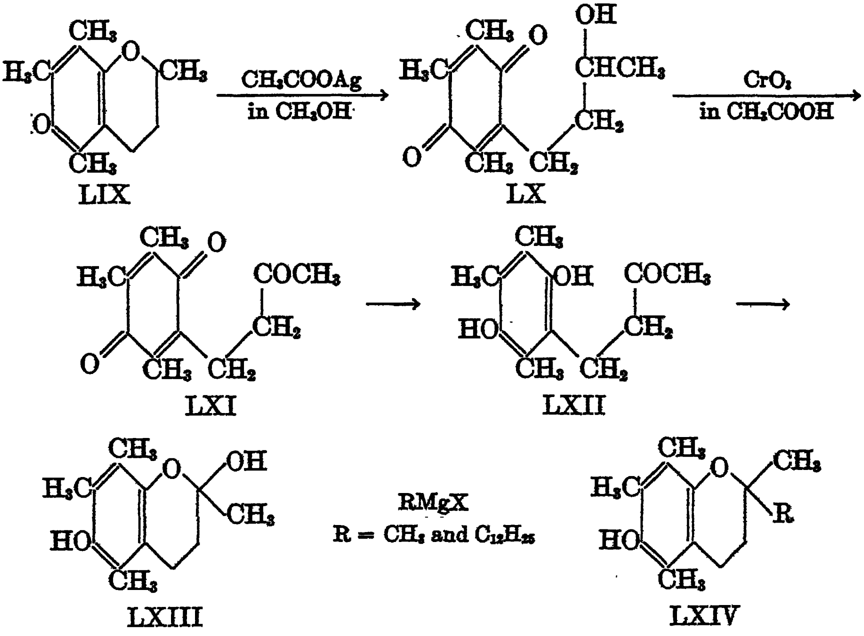
While such syntheses as these are interesting and some of them appear, from the results of model experiments, to be promising as general methods for the synthesis of *p*-hydroxychromans and *p*-hydroxycoumarans, no tocopherols have as yet been synthesized by any of these methods. Likewise unsuccessful as yet, are experiments leading to the synthesis of tocopherols without the use of phytol. The action of Grignard reagents upon dihydrocoumarins leads to α,α-disubstituted chromans (L) in which





the two substituents are the same (9, 15, 67, 107, 118, 126, 127), although by subjecting the dihydrocoumarin to the action of a mixture of two different Grignard reagents, the chroman LI can be obtained (67).

The ketone LVII has been synthesized in two different ways (66, 125), and addition of RMgX to this ketone (R = CH_3 and $C_{12}H_{25}$), followed by cleavage of the ether linkages by hydrobromic acid leads directly to the chroman LVIII (66). Finally, the introduction of the second substituent into the α-position of a *p*-hydroxychroman has been achieved, starting with the monosubstituted chroman (68), through the series of compounds LIX to LXIV. The yields in this synthesis were fair, but the synthesis cannot compare in efficiency with the direct synthesis of tocopherols from



hydroquinone and phytol or the phytyl halides. Indeed, it is difficult at present to see how any other synthesis can possibly compare favorably with the direct synthesis, for the intermediates necessary, if phytol is not used, are themselves extremely complicated and difficult to prepare (117, 120, 124). The synthesis of relatively large amounts of alkylated quinones and hydroquinones was at first a formidable task, but these preparations have been studied in two laboratories (42, 81, 116) with the result that this phase of the tocopherol syntheses may now be regarded as solved. Good yields of alkylated quinones and hydroquinones can be obtained from readily accessible methylated phenols by means of efficient processes which do not involve very many steps.

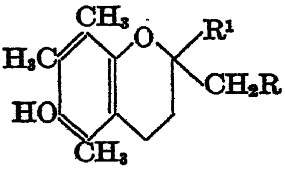
V. CHEMICAL PROPERTIES OF THE TOCOPHEROLS

The chemical properties of these substances depend upon the presence of the phenolic hydroxyl group and upon the fact that they are essentially monoethers of hydroquinones. By acylation, esters are produced and a series of these esters has been prepared (19). Among the acids used are the simple fatty acids, such as acetic and propionic acids; dibasic acids, such as succinic acid; and one of the aromatic series, benzoic acid. Some of these esters are fully as active biologically as α-tocopherol,—indeed, the acetate appears to surpass α-tocopherol in biological activity. Although many esters have been prepared, all except the allophanate, the *p*-nitrophenylurethan, and the nitrobenzoates are oils.

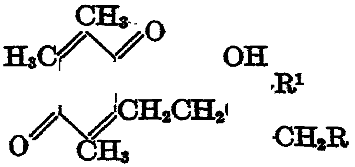
Aside from the reactions of the hydroxyl group, the chemical properties of the tocopherols center about the easy oxidation of these compounds. They show the properties of oxidation inhibitors (102), and their activity in this respect increases in the order α-, β-, and γ-, that is, the antioxidant activity is the reverse of the biological activity. The tocopherols are slowly attacked by oxygen, gradually darkening and acquiring a reddish color. They are also very sensitive to ultraviolet light (84). Not all specimens behave alike in this respect, however, and traces of impurities apparently affect the rate of oxidation very much. As the oxidation proceeds, the biological activity diminishes. The oxidation of the tocopherols is greatly retarded by the action of inhibitors such as hydroquinone or ascorbic acid, and is greatly *accelerated* when the exposed surface is increased,—i.e., when the tocopherols are chromatographed, or incorporated into finely divided powders of any sort (53). The esters, however, are stable in air over long periods of time, even when the exposed surface is greatly increased.

The oxidative degradation of the tocopherols, using permanganate or chromic acid, has already been discussed. When subjected to mild oxidation, however, no carbon is lost in the initial stages, and there results a series of compounds closely related to the tocopherols (36, 62, 64, 74, 78, 90, 114). The end product of this type of oxidation,—which is shown by all 6-hydroxychromans and 5-hydroxycoumarans so far investigated (114),—depends upon the oxidizing agent used.

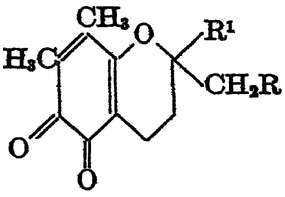
When the *p*-hydroxychroman IV (R = hydrogen, alkyl, and, for α-tocopherol, $C_{15}H_{31}$—) is oxidized by ferric chloride (62, 64, 72), gold chloride (78), silver acetate (64, 68), silver sulfate (64) or, under certain circumstances by silver nitrate, the product is the yellow *p*-quinone X. This quinone can be reduced to the hydroquinone LXV and this, in turn, can be converted either to the quinone X or the original chroman IV. When, however, the action of silver nitrate is prolonged (36, 62, 64, 78), or when nitric acid in ethanol is used as the oxidizing agent (49, 78, 114),



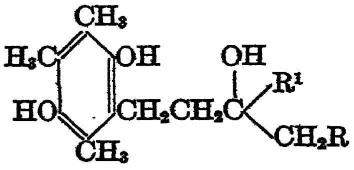
IV



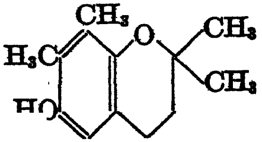
X



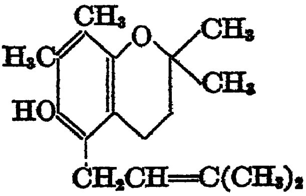
LXVI



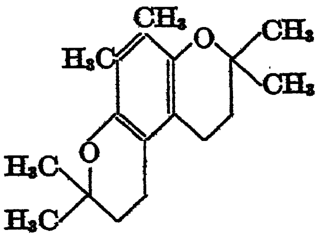
LXV



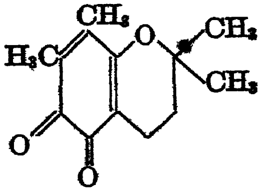
LXVII



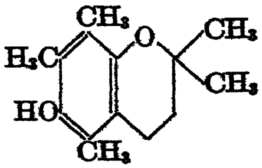
LXVIII



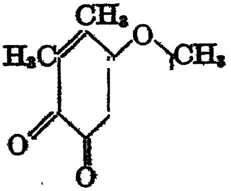
LXIX



LXX

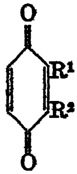


XVIII



LXXa

the reaction proceeds beyond the yellow *p*-quinone (X) stage and brilliant red solutions are obtained. From these solutions, red crystalline substances can be obtained. These substances are *o*-quinone derivatives (LXVI), formed as the result of a curious reaction in which the substituent in the 5-position of the original chroman IV has been eliminated (114). The red solids form phenazines and show other typical reactions of *o*-quinones. That it is the group in the 5-position that is eliminated in this reaction was shown by oxidation of the three substances LXVII, LXVIII, and LXIX, prepared by condensation of *o*-xylohydroquinone with isoprene. All three of these substances gave the same red crystalline oxidation product LXX; this is also the product when the chroman XVIII is oxidized in the same manner. The red oxidation product of 2,4,6,7-tetramethyl-5-hydroxycoumaran (XVI) has also been isolated (112). This substance is likewise an *o*-quinone (LXXa), but it is a much more sensitive substance than the chroman LXX. This reaction appears to be given by all chromans and coumarans which have an hydroxyl group para to the bridge oxygen, and it can be concluded that if the heterocyclic compound can be oxidized readily to a quinone of the type illustrated by LXXI (vacant positions may be occupied by alkyl or substituted alkyl groups), a red *o*-quinone of the type LXX can be obtained, with elimination of the group R^2, when the group R^1 is any of those listed in the first column below:

	GROUPS R^1 WHICH GIVE RED *o*-QUINONES	GROUPS R^1 WHICH DO NOT GIVE RED *o*-QUINONES
 LXXI	$—CH_2CH_2CHOHCH_3$	$—CH_2CH_2COOH$
	$—CH_2CHOHCH_3$	$—CH_2COCH_3$
	$—CH(C_2H_5)CHOHCH_3$	$—COCH_2COCH_3$
	$—CH_2CH_2C(OH)(CH_3)_2$	$—CH_2Cl$
	$—CH(CH_3)CHOHCH_3$	$—CH{=}C(COOH)COOC_2H_5$
	$—CH_2CH_2C(OH)(CH_3)R$	$—CH_3$
	$—CH_2CH{=}CH_2$	$—C_2H_5$

When the group R^1 is any of those listed in the second column, no red *o*-quinone can be obtained (114). It was at first supposed that these red compounds had double the molecular weight required by the simple formulas (62, 64, 78), and this is true when camphor is used as the solvent. However, the molecular weight in benzene is normal (74).

VI. METHODS OF ASSAY AND ANALYSIS FOR TOCOPHEROLS

Besides the biological assay, already discussed, and the careful measurement of absorption spectra (137), there exist a number of chemical methods for assay of materials containing tocopherols.

Potentiometric titration with gold trichloride (73, 83, 84, 85) has proved to be of great value. Since carotenoids also react with gold chloride, these must either be absent or determined independently, although the amount of carotenoids is so small in most cases that the error introduced is very slight. The method does not distinguish between α- and β-(or γ-) tocopherols, but gives the sum of all the tocopherols. Since the biological activities of the tocopherols differ, this chemical method cannot be used to replace the bioassay, although there usually is a good agreement between this method and the bioassay. A number of natural oils have been analyzed by this method; the results are shown in table 1 (83).

TABLE 1

Tocopherol content ($\alpha + \beta$) of various materials

MATERIALS	CONTENT
	per cent
Unsaponifiable fraction from wheat-germ oil*	13.4
Wheat-germ oil	0.52
Wheat germs	0.0259
Unsaponifiable fraction from corn-germ oil†	10.2
Corn germs	0.0164
Unsaponifiable fraction from lettuce‡	4.3
Lettuce (dry)	0.055
Unsaponifiable fraction from linseed oil	2.34
Linseed oil	0.023
Unsaponifiable fraction from olive oil	0.935
Olive oil	0.008
Unsaponifiable fraction from sesame oil	0.63
Sesame oil	0.005
Unsaponifiable fraction from coconut oil	0.55
Coconut oil	0.0027

* Sterols partly removed; carotenoids less than 0.1 per cent.

† Part of the sterols removed; no carotenoids present.

‡ Most of the sterols removed; corrected for 0.3 per cent carotenoids.

A second method of analysis involves the oxidation of the tocopherols with ferric chloride in ethanol; the ferrous ions so formed are converted into a red complex by addition of α,α'-dipyridyl, and the intensity of the color is measured (43). Besides α,α'-dipyridyl, α,α'-dipiperidyl or *o*-phenanthroline may be used, but the first of these gives the best straight-line relationship between color and concentration. Only 10 to 15 min. are required to determine 0.1–0.4 mg. samples using the Zeiss Pulfrich photometer with 1-cm. cell. In this method also, carotenoids interfere and a correction factor must be applied if these are present, or they must be removed by filtration of the benzene solution of the concentrate through a layer of floridin. The method is more sensitive than the potentiometric titration for very small amounts of material, although the two methods check very well and both agree well with the figures obtained by biological assay.

A third method, also colorimetric, is based upon the red color which is formed when solutions of the tocopherols in ethanol are oxidized with nitric acid under specified conditions (49). This method has the advantage that carotenoids do not interfere, but the values obtained are frequently slightly high because of the red o-quinoid oxidation products often already present in the oils. The procedure is very convenient and rapid, and the limits of the method have recently been explored (134). The structure of the compound responsible for the red color has also been determined (114). In figures 3 and 4 are shown some curves obtained by this method; it is surprising how closely the curve for the simple chroman (curve 1) follows that of α-tocopherol (curve 2). It is apparent from the differences between curves 1 to 4 (chromans) and curves 5 to 6 (coumarans) that this method provides a rapid means of distinguishing between the two classes of ring structures, provided that the compounds are hydroxylated para to the oxygen atom of the heterocyclic ring (curve 7).

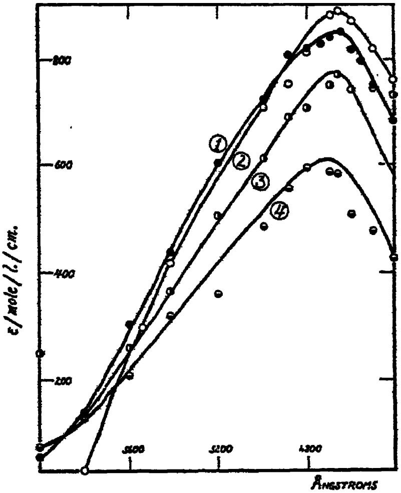


Fig. 3

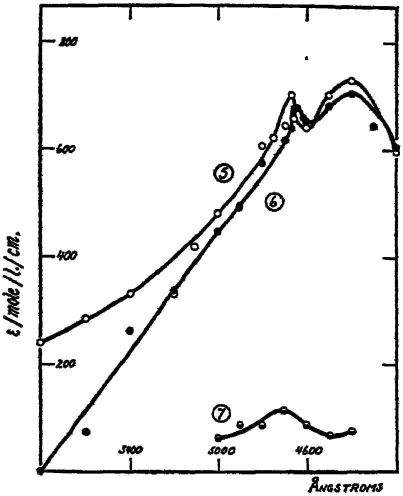


Fig. 4

Fig. 3. Absorption spectra. Curve 1, 2,2,5,7,8-pentamethyl-6-hydroxychroman; curve 2, α-tocopherol (Furter); curve 3, α-tocopherol, once distilled (impure); curve 4, γ-tocopherol (impure?).

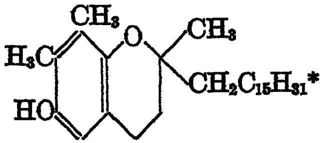
Fig. 4. Absorption spectra. Curve 5, 2,3,4,6,7-pentamethyl-5-hydroxycoumaran; curve 6, 2,4,6,7-tetramethyl-5-hydroxycoumaran; curve 7, 2,4,6,7-tetramethylcoumaran.

VII. SPECIFICITY OF VITAMIN E

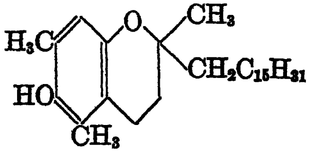
Vitamin activity is usually very specific, and even slight changes in the structure of the vitamin molecule are sufficient to reduce the biological activity greatly or to remove it completely. Contrary to the usual experience in this field, vitamin E activity is shown by a great number of compounds widely different in nature, and only slightly related in structure to the tocopherols. Over one hundred and thirty individual compounds have been assayed biologically, and a complete list of these has recently been published (37). The list of substances examined includes chromans chromenes, coumarans, coumarins, coumarones, phenols, quinones, hydroquinones, and their esters and ethers. Of the one hundred and thirty or more compounds tested, over forty show vitamin E activity. It is true that, with very few exceptions, none of these synthetic substances compares with the tocopherols in activity and many of them have to be fed at levels (50 to 100 mg.) approaching the toxic in order to obtain positive results in the bioassays, yet these results do show quite definitely that vitamin E activity is quite widespread and is by no means confined to a single class of compounds.

α-Tocopherol has been synthesized from trimethylhydroquinone and synthetic phytol (87); this product showed approximately the same activity as natural α-tocopherol. In all the tocopherol syntheses using phytyl derivatives, the product is racemic about the α-carbon atom of the heterocyclic ring; it is customary to refer to such a tocopherol as *dl*-α-tocopherol. This substance has been resolved *via* the bromocamphorsulfonates (79, 80), but the activity is unchanged. Hence symmetry or asymmetry about the α-carbon atom of the heterocyclic ring does not influence the activity of the tocopherol, nor does the optical state of any of the asymmetric carbon atoms in the phytol side chain exert any effect, since the product from synthetic phytol was as active as the natural tocopherol (87; especially 86). In fact, it appears that natural tocopherol is racemic about all three asymmetric centers (86). Synthetic α-tocopherol and its acetate are nontoxic, and very large doses (50 g. per kilogram of body weight to mice) have no ill effects (17). Nor do these substances have any carcinogenic properties (18).

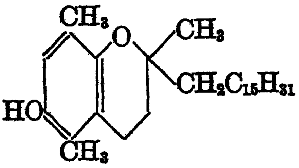
The homologs of α-tocopherol in which the homology is due to changes in the benzene ring show a decreasing activity as methyl groups are removed, or as methyl groups are replaced by ethyl groups. Thus *o*(or *dl*-γ)-, *m*-, and *p*(or *dl*-β)-xylotocopherols (LXXII, LXXIII, LXXIV) are active when fed at 5- to 20-mg. levels (37, 54a, 76, 86); the ethyl homolog LXXV is active when fed at 10- to 16-mg. levels (81, 86). The tolutocopherols (LXXVI) (isolated as a mixture; position of the methyl group undetermined) are inactive at levels of 40 to 50 mg. (54a, 76); the tocopherol with no methyl groups in the benzene ring is inactive in 50-mg. doses (54a), while 6-desoxy-*dl*-α-tocopherol (LXXVII) is inactive in 100-mg. doses (140). When the phytol side chain in α-tocopherol is



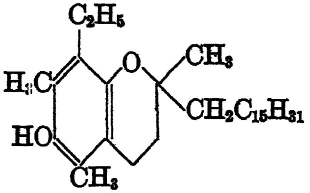
LXII



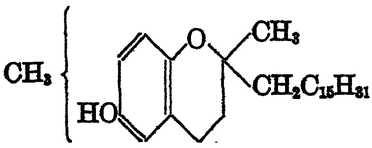
LXXIII



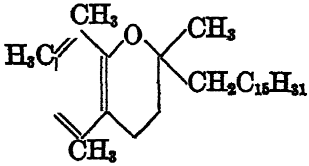
LXXIV



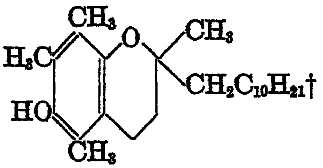
LXXV



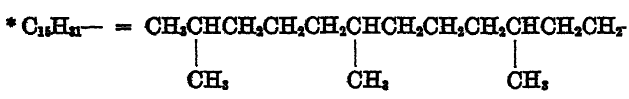
LXXVI



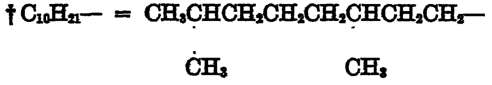
LXXVII



LXXVIII



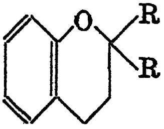
$$* C_{15}H_{31}— = CH_3\underset{\substack{|\\ CH_3}}{C}HCH_2CH_2CH_2\underset{\substack{|\\ CH_3}}{C}HCH_2CH_2CH_2\underset{\substack{|\\ CH_3}}{C}HCH_2CH_2—$$



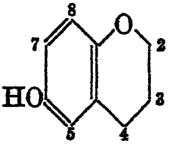
$$† C_{10}H_{21}— = CH_3\underset{\substack{|\\ CH_3}}{C}HCH_2CH_2CH_2\underset{\substack{|\\ CH_3}}{C}HCH_2CH_2—$$

shortened by one isoprene unit, the compound (LXXVIII) is inactive at the 20-mg. level (82). From these results it follows that, starting with α-tocopherol (activity 3 mg.), any change in the groups in the benzene ring, or in the nature of the long aliphatic side chain, reduces very much the activity of the compound. Further, the hydroxyl group para to the bridge oxygen is necessary for any activity, although it can be masked as any one of several *carboxylic* esters without reducing the activity appreciably (19). This hydroxyl group *cannot* be masked as the allophanate, or as an ether, without complete loss of activity.

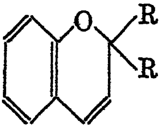
Turning to the simpler compounds, chromans represented by LXXIX



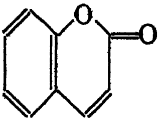
LXXIX



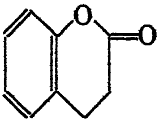
LXXX.



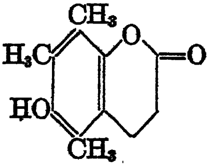
LXXXI



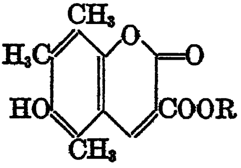
LXXXII



LXXXIII



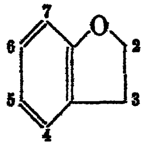
LXXXIV



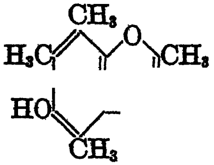
LXXXV

are active when the groups R are hydrogen (140), ethyl (37), or *n*-butyl (37), but inactive when the groups R are methyl or *n*-propyl (37). This alternation in activity with groups containing even and odd numbers of carbon atoms is very curious and it would be interesting to extend the series further. Of the other chromans with the 6-position vacant, 2,2,3-trimethyl- (37), 2-methyl-4-ethyl- (37), and 2,2,5,7-tetramethyl- (37) chromans are inactive, while 2,5,7,8-tetramethylchroman (140) is active. A number of chromans with the hydroxyl group in position 6 (LXXX) have been examined. These include 2,5,7,8-tetramethyl- (67, 82, 140), 2,2,5,7,8-pentamethyl- (37), 2,3,5,7,8-pentamethyl- (67), 2,5,7,8-tetramethyl-2-dodecyl- (60), and 2,5,7,8-tetramethyl-2-isohexyl- (37) -6-hydroxychromans, all inactive except the 2,2,5,7,8-pentamethyl compound, which in one test out of three showed a faint activity at the level of 100 mg. (37). The other 6-hydroxychromans studied are all closely related to the tocopherols, and the bioassays of these compounds are discussed in the preceding paragraph. Three chromenes (LXXXI) have been examined (37),—those in which the groups R are methyl, ethyl, and *n*-butyl. All are inactive. Of the six coumarin derivatives examined (37), coumarin (LXXXII) and dihydrocoumarin (LXXXIII) are inactive; indeed, the former is toxic at the level fed (100 mg.). The dihydrocoumarin LXXXIV, which has the same substituents in the benzene ring as α-tocopherol, is inactive. Likewise inactive are the substituted coumarins LXXXV when R is hydrogen or isoamyl, but, astonishingly, when R is ethyl the coumarin LXXXV shows a very high activity,—being effective in doses of 20 mg. This compound LXXXV, R = C_2H_5, is the most active compound known outside of the tocopherols themselves; the activity exceeds that of tolutocopherol (LXXVI) and is comparable to that of the xylotocopherols (LXXII, LXXIII, and LXXIV). This high activity of a compound quite different in structure from the tocopherols is very mysterious, and it becomes all the more inexplicable in view of the inactivity of the two closely related substances obtained when the ethyl group (R) in LXXXV is replaced by hydrogen or isoamyl.

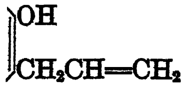
Several compounds with the heterocyclic ring consisting of five instead of six atoms have been examined. These are for the most part coumarans (LXXXVI), although one coumarone (LXXXVII) has been studied and it is inactive (37). Of the coumarans, the unsubstituted molecule (LXXXVI) is inactive (140). 2-Methylcoumaran showed great activity



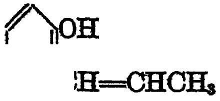
LXXXVI



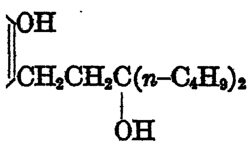
LXXXVII



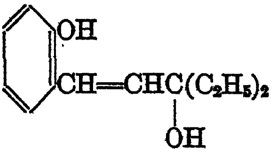
LXXXVIII



LXXXIX



XC



XCI

at a level of 50 mg. in one of four assays; the other three assays (25, 50, and 100 mg.) were negative (37). 2,2,7-Trimethylcoumaran was also active (37), as was 2,3,4,6,7-pentamethyl-5-hydroxycoumaran (37), while 3-methyl- (37), 2,4,6,7-tetramethyl- (37), 2,4,6,7-tetramethyl-5-hydroxy (37, 140), and 4,6,7-trimethyl-2-*n*-heptadecyl-5-hydroxy- (9) coumarans were all inactive.

Some phenols—mostly containing allylic groups—have been studied

(37), since these are possible intermediates in the syntheses of chromans and coumarans from allylic compounds. *o*-Allylphenol (LXXXVIII) is inactive in 25-mg. doses, but active when the dose is 50 mg. *o*-Propenylphenol (LXXXIX) is inactive. A di-*o*-hexenylphenol (mixture of isomers) is active, as is *p*-amino-*o*-allylphenol. All the other phenols tested are inactive; these included *o*-α-methylallyl-, *o*-hexenyl-, 2,3,5-trimethyl-6-allyl-, *p*-capryl-, *p*-*tert*-octyl-, *o*-allyl-*p*-carboxy-, *o*-allyl-*p*-carbethoxy-, and two more complicated phenols (XC and XCI).

By far the most extensively investigated compounds, however, are the quinones and hydroquinones, together with esters and ethers of the latter. These compounds were examined in some detail, because early in the work on the structure of vitamin E there was some evidence which indicated that possibly the vitamin might be a monoether of a methylated hydroquinone. With one exception, the *p*-quinones studied are all inactive. These include duroquinone (36, 65), tetraethylquinone (toxic) (37), thymoquinone (toxic) (37), trimethylethylquinone (37), 1,4-naphthoquinone (140), 1,2-naphthoquinone (toxic) (37), 2,3-dimethyl-1,4-naphthoquinone (37, 140), 2-methyl-1,4-naphthoquinone (37), 2-hydroxy-1,4-naphthoquinone (37), 2-methoxy-1,4-naphthoquinone (37), anthraquinone (37), and β-methylanthraquinone (37). The one exception to the inactive *p*-quinones is α-tocopherylquinone (X), obtained by mild oxidation of α-tocopherol, and the results of different workers who have tested this substance do not agree. It has been reported active once (35), but three other assays were negative (62, 140). The red *o*-quinone oxidation product of α-tocopherol (LXVI; $R^1 = CH_3$, $R = C_{15}H_{31}$) is inactive in doses of 3 and 6 mg., but active in doses of 12 mg. (37).

Of the hydroquinones examined, the unsubstituted hydroquinone is inactive (36), as is *m*-xylohydroquinone (37, 140), but *o*-xylohydroquinone is active (139), while *p*-xylohydroquinone is inactive in 50-mg. doses (37) but active in 100-mg. doses (140). Trimethylhydroquinone has been reported as inactive (100 mg.) (37) and also active at this same level (140). Durohydroquinone is active (65, 68), while trimethylethylhydroquinone and trimethyl-5-acetohydroquinone are inactive (138, 140). The only naphthohydroquinone tested is 2,3-dimethyl-5,6,7,8-tetrahydro-1,4-naphthohydroquinone; this compound exhibits good activity (139), as does its mono-*n*-dodecyl ether (65).

Table 2 shows the results obtained with a series of esters and ethers of trimethylhydroquinone.

Table 3 shows the results obtained with a series of esters and ethers of tetramethylhydroquinone (durohydroquinone).

Three simple phenol ethers,—phenylhexenyl ether, phenylcinnamyl ether, and *p*-carboxyphenylallyl ether,—have been examined (37); all are inactive. A ketone, 4-(2,5-dimethoxy-3,4,6-trimethylphenyl)-2-butanone, is likewise inactive (37). Finally, phytol, alone or in combination with trimethylhydroquinone, shows no activity (37); hence, even though the synthesis of α-tocopherol from these compounds in the laboratory is surprisingly easy, the synthesis does not occur *in vivo*, at least when the substances are fed.

TABLE 2

Ethers and esters of trimethylhydroquinone

DERIVATIVE	ACTIVITY	REFERENCE
Monobenzoate	+	(140)
Bis-β-iodopropionate	−	(140)
Mono-*n*-hexyl ether	+	(139)
Mono-*n*-dodecyl ether	+	(139)
Mono-*n*-dodecyl ether acetate	+	(139)
Monodihydrochaulmoogryl ether	+	(139)
Di-*n*-dodecyl ether	−	(139)

TABLE 3

Ethers and esters of tetramethylhydroquinone

DERIVATIVE	ACTIVITY	REFERENCE
Mono-*n*-butyl ether	+	(139)
Di-*n*-butyl ether	+	(139)
Mono-*n*-hexyl ether	+	(139)
Di-*n*-hexyl ether	+	(139)
Mono-*n*-heptyl ether	−	(139)
Di-*n*-heptyl ether	+	(139)
Mono-*n*-octyl ether	+	(139)
Di-*n*-octyl ether	+	(139)
Monocetyl ether	+ (twice); − (once)	(36, 46)
Monododecyl ether propionate	−	(139)
Monododecyl ether palmitate	+	(139)
Monododecyl ether	+	(36, 46, 139)
Didodecyl ether	−	(139)
Monohydrophytyl ether	+	(139)
Mono-*n*-octadecyl ether	−	(36, 46)
Mono-*n*-nonadecyl-2 ether	+	(36, 46)
Mono-2-methyloctadecyl ether	−	(36, 46)
Mono-*n*-nonadecyl ether	+	(140)
Di-*n*-nonadecyl ether	−	(140)
Mono-3-methyl-5-(1′, 1′, 3′-trimethyl-2′-cyclohexyl)pentyl-1 ether	−	(140)
Monodihydrochaulmoogryl ether	+	(139)
Monobenzyl ether	+	(139)
Dibenzyl ether	+	(139)

From the results of the bioassays presented here, it is clear that many compounds exhibit some vitamin E activity, and there are one or two fairly simple compounds which show considerable activity. These results, until recently at variance with all other results in the vitamin field, appear now to be paralleled in the field of the K vitamins, where a number of substances aside from the vitamins themselves possess great potency. Notable among these are certain 1,4-naphthoquinones, especially 2-methyl-1,4-naphthoquinone. None of these naphthoquinones possesses any vitamin E activity, but the methylnaphthoquinone has about as much antihemorrhagic activity as vitamin K_1 itself.

There is no adequate theory at present to account for vitamin E activity in terms of organic structure. One theory has been advanced (37, 62, 67) independently from two laboratories, but there remain objections to the theory which will have to be overcome before it can be accepted (37, 62, 67, 71).

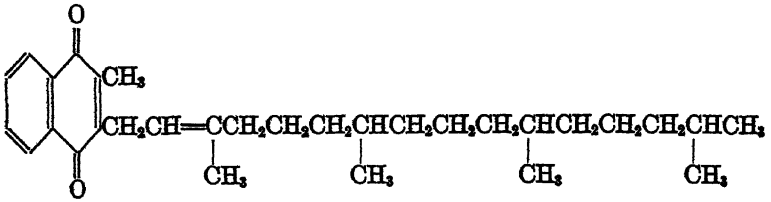
VIII. USES AND IMPORTANCE OF VITAMIN E

Vitamin E appears to be a most promising substance to be used in the treatment of habitual abortion in women, and for similar use in the veterinary field. Some rather startling successes have been reported when the vitamin has been used in these cases. There is good evidence also that the young of both sexes need vitamin E for normal growth, and that there is some connection between the amount of vitamin E and the functioning of the thyroid gland as well as that of the hypophysis. That muscular dystrophy can result from a lack of vitamin E appears to be well established (106). The writer is not competent to discuss this field, and since reviews covering the use of vitamin E in medicine have recently been published (6, 23, 50, 56, 59, 61, 69, 70, 93, 94, 135; especially 50, 61) only the most general statements have been made here. Most of the studies so far have been carried out using wheat-germ oil concentrates, but now that the synthetic vitamin is available in pure form, a standard preparation of known potency is available and it is to be hoped that the clinical work will proceed rapidly so that the usefulness, as well as the limits, of vitamin E therapy may soon be known.

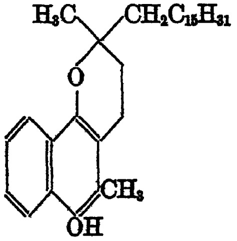
IX. VITAMIN K

Before closing this review, a word about vitamin K may not be out of place, for this vitamin is unique in that it is the first of all the vitamins whose chemistry has been aided and simplified by the chemical knowledge gained in the study of any other vitamin. Until the recent work on the structure and synthesis of vitamins E and K, no vitamin had ever been found which was in any way related chemically to any other vitamin,—

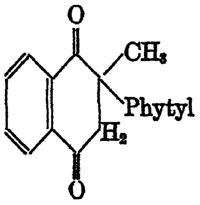
each vitamin belonged to an entirely different class of chemical compounds; indeed, vitamins A and D might almost be said to have represented, at the time they were isolated, new classes of organic compounds. Vitamins E and K, however, are closely related in their chemistry, and the knowledge and experience gained in studying one of these vitamins has been of great value in the study of the other. There are two K vitamins, K_1 (XCII) and K_2, both of which show a powerful antihemorrhagic activity, although K_1 surpasses K_2 in this respect (16a).



XCII
Vitamin K_1



XCIV



XCIII

Vitamin K_1 has been synthesized in two laboratories (12, 47, 48). However, the methods used for the synthesis of vitamin E had to be modified considerably in order to avoid ring closures which would lead to compounds of the tocopherol type. The yield of vitamin K_1 from phytol and 2-methylnaphthohydroquinone was good (132); very little of the naphthotocopherol (XCIV) was produced, but relatively large amounts of a by-product, probably XCIII, resulted (132). Unfortunately it has not been found possible to convert compounds of the tocopherol types into compounds of the vitamin K types, although the reverse transformation has been realized in the transformation of vitamin K_1 (XCII) into the naphthotocopherol XCIV (48a). Vitamins E and K also have in common the fact that the specificity is not limited to the vitamins themselves,—indeed, 2-methyl-1,4-naphthoquinone appears to be much more active than vitamin K (16a). Curiously enough, no compounds have been found so far which show both kinds of activity: if a substance exhibits vitamin E activity, it does not show any vitamin K activity, and *vice versa* (but in this connection, see references 16a, 54a, 91a).

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[2] References 6, 23, 50, 56, 59, 61, 69, 70, 93, and 94 are review articles; the whole issue of *Angewandte Chemie* **52**, 413 32 (July 17, 1939) was devoted to the review articles of John (59) and Grandel (50), and to a verbatim report of the Vitamin E Conference held in London on April 22, 1939 (135). The papers given at this Conference, together with the discussions that followed, have been printed in book form (136). Those interested in the physiological aspects of vitamin E will find the position of such matters as of April, 1939, well defined in this book. For a more detailed review of this book, see reference 108. Of the above references to review articles, those of fairly recent date, which deal particularly with the physiological aspects of vitamin E, are 50, 61, and 69.

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Notes added to proof, September 24, 1940

1. Karrer and Geiger (Helv. Chim. Acta 23, 455 (1940)) have published a very careful study of the yellow α-tocopherylquinone (X). The quinone was prepared by oxidation of tocopherol using three different reagents: (*a*) gold trichloride, (*b*) ferric chloride, and (*c*) silver nitrate. The quinone prepared by method a contained no reducing substances. It was a golden-yellow oil which gave a very good absorption spectrum curve, and the authors believe it to be "the only homogeneous preparation of this quinone described in the literature." The quinone prepared by method b contained considerable α-tocopherol or other reducible substance. After 6 hr. contact with the reagent, 11.6 per cent of α-tocopherol was still present, and after 36 hr., 7 per cent. (Analytical values were obtained by potentiometric titration, as well as by the method of Emmerie and Engel). This product was again subjected to the action of ferric chloride, and the second treatment led to a product showing no reducing properties. It is interesting that the reducing substance cannot be completely removed by one treatment with ferric chloride, no matter how prolonged. The product obtained by method c contained α-tocopherol, the yellow quinone X, and the red *o*-quinone. The products obtained by methods a and b were

tested biologically at levels of 10 and 25 mg. Absolutely no activity was shown; hence it is unlikely that α-tocopherol owes its activity directly to any oxidation–reduction system in the body.

2. Karrer, Jaeger, and Keller (Helv. Chim. Acta **23**, 464 (1940)) have determined the tocopherol content of certain animal organs. The liver (horse, cattle) shows the highest content of tocopherol, but the vitamin is present also in the muscle, heart, and kidney.

3. Karrer and Yap (Helv. Chim. Acta **23**, 581 (1940)) have prepared the chroman IV, in which R = isoamyl,—that is, the substance which contains two "isoprene units" less than α-tocopherol in the side chain. This substance shows no bio-activity at a level of 40 mg.

4. Tishler, Fieser, and Wandler (reference 132, page 1984, footnote 6a) report that the naphthotocopherol XCIV shows vitamin E activity at the 25-mg. level and that this compound also possesses moderate vitamin K activity (between 300 and 600 γ). This is the first instance of any compound combining the biological actions of two vitamins.

A REVIEW OF THE KJELDAHL DETERMINATION OF ORGANIC NITROGEN

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CONTENTS

I. INTRODUCTION

During the fifty-odd years which have passed since the inception of Kjeldahl's (57) method for determining organic nitrogen, considerable progress has been made. That this is true is borne out by the amount of literature on the subject.

Originally, the method was designed for the brewing industry as an aid in following protein changes in grain during germination and fermentation. Its use soon became widespread and can now be regarded as an important tool of analytical chemistry. Fundamentally, it is a wet oxidation employing concentrated sulfuric acid as a digestion medium, and resulting in the formation of ammonium sulfate which is subsequently distilled with an excess of alkali. The ammonia thus formed is determined by any one of several available methods.

Prior to Kjeldahl's method, however, concentrated sulfuric acid had been used for preliminary treatment of organic material before completing the determination of nitrogen by the now obsolete Will–Varrentrapp method. Wanklyn (140) had used alkaline permanganate for the determination of protein nitrogen, and Kjeldahl, following along this line, concluded that the formation of ammonia would take place more easily in an acid medium. Experimental evidence showed this to be the case, and that the use of concentrated sulfuric acid was necessary.

Many improvements and modifications of the method followed, after its value was established. Primarily devised for the determination of protein nitrogen, the method has been extended to include the determination of various other forms of nitrogen.

From the abundance of available data, any attempt at correlation must be made through the medium of classification, and in the following data, the component parts of the Kjeldahl method will be discussed under their respective headings.

II. DIGESTION MEDIA

In Kjeldahl's original method, sulfuric acid alone was used as a digestion medium. The principal objections to this procedure were the length of time for digestion, and the necessity of using a small sample in order not to prolong the digestion. To increase the severity of the reaction and reduce the digestion time, Gunning (48) in 1899 proposed the use of potassium sulfate as a means of raising the boiling point of the digestion mixture. This procedure is standard practice. However, one fact should be borne in mind,—namely, that when the composition of the residue approaches that of the acid sulfate, the tendency is to lose ammonia. The residue in the flask after digestion should not solidify on cooling.

P. A. W. Self (119) stated that ammonia is almost completely volatile under these conditions, and, further, that if 25 cc. of sulfuric acid and 10 g. of potassium sulfate are used in the digestion, at least 15 g. of sulfuric acid should remain in the flask, approximately 6.7 g. of acid being consumed to form the acid sulfate. This loss of ammonia was confirmed by Carpiaux (14). Prolonged boiling and too rapid distillation of acid should be avoided. It may sometimes be necessary to stop the digestion in order to add more acid.

The amount of acid necessary to digest 1 g. of organic matter varies, of course, with the type of material under examination. It has been found (119) by experiment that 1 g. of carbohydrate requires approximately 7.3 g. of sulfuric acid for complete oxidation, 1 g. of protein requires 9.0 g., and 1 g. of fat 17.8 g. of sulfuric acid.

The use of sodium sulfate as a substitute for potassium sulfate has been suggested and reported upon from time to time. Latshaw (62) made a comparison of the two, and showed that when an equivalent amount of sodium sulfate was used, no difference in results was noticed. On the other hand, Brill and Agcaoli (12) were unsuccessful in their attempt to substitute one for the other. Various other workers (4, 25, 78, 97, 136), however, have reported favorably upon its use.

An investigation of the Kjeldahl method by Phelps (98) showed that the proportion of either sulfate to sulfuric acid must be carefully regulated in order not to cause volatilization of ammonia, and, with highly refractory compounds, the use of sodium sulfate is not recommended unless the conditions can be very closely controlled. Later work by Daudt (21) confirmed the fact that the acid-sulfate ratio was important. A comparison of lithium, sodium, and potassium sulfates (68) showed that the potassium salt was most effective.

The effect of sodium pyrophosphate in the determination of nitrogen in gelatin has been investigated (8), and this salt has been shown to be less efficient than potassium sulfate. The substitution of most of the potassium or sodium sulfate (ten-sixteenths) by dibasic potassium phosphate (K_2HPO_4) (40) shortened considerably the digestion time of samples containing protein nitrogen. Low results, however, were obtained when all the alkali sulfate was replaced by the phosphate.

Phosphoric acid (33, 34, 35, 66, 67, 110, 126, 145) in combination with sulfuric acid has also been used as a digestion medium in both macro and micro Kjeldahl methods. Rapid digestions are possible, and such combinations are sometimes helpful where complete digestion by ordinary methods is impossible.

The clearing of the digestion mixture is not necessarily an indication that all the nitrogen has been converted to ammonia. The possibility of the formation of amines has been investigated. Villiers and Moreau-Talon (139) stated that too energetic oxidizing agents, under the influence of temperature, concentration, and time of heating, promote the formation of amines. Gortner and Hoffman (44) found that approximately 7 per cent of the distillate from a Kjeldahl-Gunning digestion could be amine nitrogen, and also that magnesium, calcium, strontium, and barium salts influenced the amount of amines formed.

Many workers have recommended an after-boil ranging from 0.5 to 3 hr., in special cases even longer than this. In contradiction to this, it has been shown (5) that in the case of rice or wheat flour, oatmeal, and bone meal, it is not necessary to continue digestion after the solution has cleared. On the other hand, the period of after-boil in determining nitrogen in coal varies from 18 min. to 235 hr. An investigation by Crossley (19) into the relative merits of mercuric oxide and selenium as digestion catalysts brought out the fact that a definite minimum time of after-boil was necessary.

III. OXIDIZING AGENTS

Regardless of the fact that sulfuric acid is a strong oxidizing medium, it is often necessary to increase the severity of the reaction. Two substances that have merited a great deal of attention are potassium permanganate and hydrogen peroxide.

From the evidence presented by various authors, the suitability of permanganate is questionable. Siegfried and Weidenhaupt (121) have stated that if the permanganate is added in small amounts to the digestion mixture and then brought to a boil, there is no danger of loss of ammonia. With certain substances, it is essential to boil after each addition. Oxidation is complete if there is no decolorization after boiling for 3 min. In the determination of nitrogen in coal, Fieldner and Taylor (31) reported no loss of ammonia, and that no modification for nitrates or nitro compounds was necessary. Cochrane (16, 17) also found that lower results were obtained without the use of permanganate. In the analysis of soil and grass, Ashton (4) found that the addition of 5 g. of permanganate after the clearing of the digestion mixture gave good results with soils, but low results with grass.

On the other hand, Frear, Thomas, and Edmiston (38) found a loss of nitrogen to occur if permanganate is added immediately after the source of heat is removed, but if the temperature is allowed to fall 100°F. (in approximately 2 min.), no loss of nitrogen is observed if the permanganate is added at this time.

Phelps (99), Paul and Berry (97), and Beet (6) stated that permanganate gives low results or that it is unnecessary. Its use has been discontinued, owing to the uncertainties involved.

Hydrogen peroxide has been used for both macro and micro digestions. The reaction is more or less violent and needs to be handled carefully. The conditions under which the peroxide is added vary somewhat. Kleeman (58) and Heuss (51) treated the sample with 25 cc. of hydrogen peroxide and added 40 cc. of concentrated sulfuric acid. Koch and McMeekin (60) reported that the addition of 30 per cent peroxide to concentrated acid causes a very rapid oxidation with complete retention of nitrogen as ammonia. A 20-min. heating with sulfuric acid and 5 per cent of acid containing sulfur trioxide was recommended by Saccardi (112), after which peroxide to the amount of 10 per cent of the sulfuric acid is added. Provvedi (105) noted that digestion took place in 45 min., but attributed the activity of the hydrogen peroxide to other agents reacting with the sulfur dioxide produced by the reduction of the sulfuric acid.

The fact that no loss of nitrogen has been reported with the use of peroxide makes its use acceptable as an oxidizing agent, albeit a very active one.

Brief mention should be made of perchloric acid. Parker and Terrill (95) have used perchloric acid successfully in the Kjeldahl determination of nitrogen in leather, and Mears and Hussey (75) have reported that it aids digestion, decolorization taking place in a very short time.

On the other hand, LeTourneur-Hugon and Chambionnot (64) stated that while perchloric acid appreciably shortens digestion time, all methods of using it are not suitable. They recommended addition of the acid, a few drops at a time, during boiling, whereby complete decolorization is effected in a few minutes.

IV. CATALYSTS

The search for catalysts to produce a further increase in the velocity of the reaction has led experimenters through a large part of the Periodic System.

One of the earliest catalysts was platinic chloride, used by Ulsch (137) in 1886, who reported that it was satisfactory except when excessive amounts were used. Anderson (2) found that a loss of nitrogen occurred when platinic chloride was used as a catalyst in the determination of nitrogen in urine, milk treated with pepsin or trypsin, old albumin solutions, or hydrolyzed casein, but not in determinations with milk, serum, or fresh albumin solutions. He suggested that this loss might be due to the combination of the chlorine set free with the amino groups, and that this combination cannot take place with nitrogen in peptide combinations. He also found that nitrogen compounds containing chlorine could be accurately determined.

A catalyst which has been used since the beginning of the Kjeldahl method is mercury, either in the form of the metal, oxide, iodide, or sulfate, or in combination with various other compounds. From the point of view of speed, it is one of the most efficient catalysts. In 1885 Wilfarth (142) reported on a number of compounds used as digestion catalysts. He found that, while mercuric oxide was fast and effective, its tendency was to hold back the ammonia upon distillation. This is, of course, to be expected, since mercury forms complexes with ammonia. It is necessary, therefore, to convert the mercury to some compound that will cause no interference. This is accomplished by the use of alkali sulfide (22, 142), sodium thiosulfate (22, 104), monosodium phosphate, and potassium xanthate (90). Even potassium arsenate (55) has been used. Of these compounds, probably potassium sulfide (or sodium sulfide) and sodium thiosulfate are the most common. Of the other compounds studied by Wilfarth, the copper oxide was stated to be less efficient than mercury, while ferric oxide, bismuth trioxide, stannic oxide, lead dioxide, and Pb_3O_4 were not recommended.

Phelps and Daudt (100) (1919), studying the determination of nitrogen in refractory organic compounds, reported that mercuric oxide was superior to cupric sulfate, but that alum, nickel sulfate, zinc chloride, manganous chloride, manganese dioxide, and tungstic, molybdic, titanic, and vanadic acids could not be recommended.

The use of mercurous iodide has been suggested by Sborowsky and Sborowsky (116). They claimed that carbonaceous material is oxidised much more readily than if mercury alone is used as the catalyst. This was confirmed by Richards (109), who used it in the Kjeldahl digestion of leather and coal.

In refutation of the statement of Sborowsky and Sborowsky, Hassig

(50) stated that the digestion is not hastened by the use of mercurous iodide, and that there is the disadvantage of the sublimation of the iodide in the neck of the flask.

Copper, alone, or as the oxide or sulfate, is another example of a catalyst universally accepted for the Kjeldahl determination. The efficiency claimed for it is less than that of mercury, hence it is necessary to increase the digestion time. The efficiency of copper sulfate, mercuric oxide, and potassium sulfate in sulfuric acid as a digestion mixture was confirmed by Trescott (135) and was recommended for adoption as an official method by the Association of Official Agricultural Chemists.

Arnold and Widemeyer (3), in 1892, reported that the use of a mixture of copper sulfate and mercuric oxide shortened the digestion time, and later Bredig and Brown (11) (1903) claimed that the mixed catalyst was more efficient than either one used alone. Powdered copper (56), also, has been used, but it seems reasonable to assume that there is no particular advantage to be gained over copper sulfate, since this compound is formed on addition of the copper to the sulfuric acid. There is also the distinct disadvantage of having to prepare the pure copper.

A more recent catalyst is selenium, used as such, or in the form of the dioxide (SeO_2) or the oxychloride ($SeOCl_2$), and either alone or in combination with various other catalysts.

First mention of selenium was made by Lauro (63), who used both selenium and selenium oxychloride as catalysts in the determination of nitrogen in flour. Rich (108) reported on the use of selenium oxychloride in combination with copper in the determination of total protein, and stated that it reduced the total time of the analysis by at least half an hour, as compared with copper alone.

A series of determinations made on a high-protein flour and on ground bran by Sandstedt (114), using (*1*) copper and mercuric oxide and (*2*) copper and selenium, showed that digestion was complete in 45 min. with copper and selenium and in 1 hr. with copper and mercuric oxide. This author stated that there appears to be greater danger of losing nitrogen by extremely long digestion with selenium than with other catalysts. An added advantage of selenium is that it is unnecessary to add a precipitant before distilling.

Comparative experiments by Crossley (19) with selenium and with mercuric oxide showed that the time of digestion was appreciably shortened. Messman (78), Tennant, Harrell, and Stull (133), and Belov and Pakhomova (7) also confirmed the efficiency of selenium.

Osborn and Krasnitz (93) stated that while selenium, or selenium oxychloride, may claim a slight advantage over copper sulfate, there is no advantage over mercuric oxide. The combination of selenium with mercuric oxide is more efficient than either alone. They recommended the use of elemental selenium rather than the oxychloride. Further comparisons were made by these authors on a wide variety of substances to determine the relative catalytic speeds of selenium, mercuric oxide, selenium and mercuric oxide, and selenium and copper sulfate. Selenium and mercuric oxide was found to be 25 per cent faster than mercuric oxide; selenium alone, and selenium and copper sulfate were less effective than mercuric oxide. Extending the digestion period increases the danger of loss of nitrogen in the following order: mercuric oxide, selenium, and selenium and mercuric oxide. They stated that this loss can be obviated by the addition of larger quantities of sulfuric acid.

The catalytic action of red mercuric oxide, selenium, selenium dioxide–copper, and selenium oxychloride in the determination of protein in wheat was discussed by Snider and Coleman (127), who found that when from 75 to 250 mg. of selenium are substituted for 0.5 g. of mercuric oxide, low values for nitrogen are obtained in the evaluation of the crude protein content of wheat, and, further, that a combination of 0.3 g. of selenium dioxide and 0.05 g. of copper in place of 0.5 g. of mercuric oxide reduced the time of determination by about 15 to 20 per cent. Goswami and Ray (45) used selenium and yellow mercuric oxide as a catalyst for the digestion of milk, whey, lymph, and protein-containing substances, and reported a substantial reduction in time, as compared with other catalysts. Selenium oxychloride (0.2 cc.) showed no advantage over mercuric oxide. A combination of 0.1 g. nickel and 0.1 g. selenium, while inducing a rapid clearing of the digestion mixture, gave low protein determinations.

It has been suggested by Illarionov and Soloveva (53) that the catalytic effect of selenium and tellurium is due to the formation of H_2SeO_3 and H_2TeO_3 in the hot sulfuric acid, and that these acids act as carriers of oxygen. The catalytic effect is proportional to the quantity of selenium or tellurium used. In a recent paper, Sreenivasan and Sadasivan (130) showed that the efficiency of selenium as a catalyst was greatly increased by the addition of mercuric oxide. They explained this in the following manner: The catalytic action of selenium in the presence of mercuric oxide depends upon the reaction

$$\text{selenium} \rightarrow \text{selenious acid} \rightleftarrows \text{selenic acid}$$

As long as oxidizable material is present, the reaction proceeds to the right, and goes to completion when all organic matter has been oxidized. Selenium alone proceeds according to the following reaction:

$$\text{selenium} \rightleftarrows \text{selenious acid}$$

Since the speed of the reaction in either direction shows no pronounced difference, the efficiency as a catalyst is much less than with mercuric oxide.

In a comparison of ferrous sulfate–selenium (9) and copper sulfate–selenium, it was found that the former possessed a slight advantage.

Davis and Wise (23)[1] have stated that selenium does not appear to be as universally adaptable to general laboratory conditions as mercury, and that its use in combination with catalysts, especially mercury, is to be discouraged.

Copper selenite dihydrate as a single catalyst has been used by Schwoegler, Babler, and Hurd (118), who found that the digestion time was considerably reduced.

Many other authors have presented definite evidence that selenium alone, or in combination, is an effective catalyst.

The preceding statements do not by any means cover the field of catalysts. This is extensive, and in many instances the catalysts mentioned exert a specific action. Brief mention will be made of a few.

The use of vanadium pentoxide as a catalyst was recommended by Oefele (92), who regarded it as an oxygen-carrier. Marino and Gonelli (74) reported that it shortened digestion time. In the Kjeldahl digestion of flour, Parri (96) found that the digestion time was considerably reduced when a mixture of 0.1 g. of vanadium pentoxide and 0.5 g. of cupric oxide was used as a catalyst. With either catalyst alone, the time was 6 hr., but a mixture of the catalysts required only 2.2 hr. for clearing. The addition of oxides of vanadium, nickel, and antimony as catalysts in the analysis of piperidine by Brill and Agcaoli (12) was found to be unsatisfactory. The work of Margosches and Lang (69) showed vanadium to be of doubtful efficiency. These same authors used tungsten (WO_3) and copper oxide, also ceric oxide, as catalysts with fairly satisfactory results.

Metallic cadmium was reported by Saiko-Pittner (113) to be a very satisfactory catalyst for pyramidon.

Dakin (20) first used potassium persulfate, $K_2S_2O_8$, which, by its decomposition, increases the effect of the sulfuric acid. The following year Milbauer (80) confirmed this, and years later, both Pittarelli (101) and Wong (147) reported on its efficiency.

Manganese dioxide (132) and potassium perchlorate (39) have been used, the latter giving satisfactory results in the digestion of leather.

In a survey made on the comparative digestion times of (*1*) cupric sulfate, (*2*) mercuric oxide, (*3*) cupric sulfate, mercuric oxide, and selenium, and (*4*) cupric sulfate, mercuric oxide, selenium, and hydrogen peroxide, Poe and Nalder (102) found that the addition of peroxide appreciably decreased the time of clearing. A comparison of several catalysts (89) used in the digestion of oil-cake samples showed mercuric oxide to be

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[1] Report of the Sub-Committee on Selenium as a Kjeldahl Catalyst in the Cereal Laboratory.

more efficient than selenium, and copper sulfate less efficient than either of these.

The accelerating and retarding action of various elements was studied by Ranedo (106), who showed that elements in the third and fourth groups of the Periodic System retard attack considerably. If accelerator elements are present, this effect is overcome. Selenium and sufficient platinum are among the most active accelerators.

The effect of each of thirty-nine metals on the determination of nitrogen in a gluten flour, studied by Osborn and Wilkie (94), showed that mercury was the most satisfactory. Of the thirty-nine metals, ten or twelve catalyzed the digestion, and the best catalysts appear to be mercury, tellurium, titanium, iron, and copper. Under less violent conditions selenium, molybdenum, vanadium, tungsten, and silver were found suitable. Larger amounts of selenium and vanadium interfere with the accuracy of the determination. Platinum also interferes.

Milbauer (81, 82, 83, 84, 85, 86) has made extensive investigations on the oxidation of organic substances with sulfuric acid. The mechanism of the digestion was studied through the medium of simple substances. The relative activities of the catalysts employed varied with the temperature and the type of compound being oxidized. Experiments performed with sucrose and a large number of metals as catalysts showed that selenium dioxide and mercuric sulfate (1:1) and selenium dioxide and cupric sulfate (3:1) were most effective. Mixtures of the catalysts are less satisfactory. In a recent communication, this author (87) has shown that, of twenty-five catalysts, mercuric sulfate–selenium promotes the most rapid digestion when the ratio of mercury to selenium is 4:1. A further reduction of time is obtained by the addition of an oxidizing agent. Addition of phosphorus pentoxide to the mercury–selenium catalyst reduces digestion time to 3.5 per cent of the time required with concentrated sulfuric acid alone. Equilibrium states and the reaction of the Kjeldahl digestion in a current of gases have also been studied by Milbauer.

V. DISTILLATION AND DETERMINATION OF AMMONIA

The preparation of the digestion mixture for distillation, and subsequent absorption of the ammonia evolved, is largely mechanical, rather than chemical, in nature. The numerous manipulative details will not be discussed here, since these can usually be left to the operator's discretion. No space will be devoted to discussion of the various modifications of the apparatus.

One of the first means of recovering the ammonia was by steam distillation. This has been more or less a controversial subject, inasmuch as some investigators have reported high values due to entrainment of alkali which was carried over into the absorption flask. Aeration, also, has been employed as means of driving off the ammonia. However, low results are obtained unless a large excess of alkali is used. Generally speaking, heat distillation is probably the most common means of ammonia recovery.

An investigation by Merlo (77) on the removal of ammonia by aeration showed that, at room temperature, the ammonia from 20 cc. of 5 per cent ammonium chloride solution was completely removed in 1.5 hr., and at 40°C. in 45 min. The rate at which air was passed through the solution was 600 to 700 liters per hour. Kober and Graves (59) stated that the amount of ammonia left in the distillation residue after aeration for an hour is negligible, and that the completeness of the distillation is independent of heat. An absorption flask devised by Sjöquist (125) allows addition of standard acid without opening the system. The following results were obtained by aeration:

TIME	AMMONIA RECOVERED
	per cent
20 min.	12.0
60 min.	32.5
4 hr.	84.5
9 hr.	98.5
11 hr.	100.0

Experiments were carried out by Falk and Lugiura (30), according to conditions stated by Kober (59), and a comparison made of aeration and heat distillation methods. For many substances the aeration method gave low results, but subsequent steam distillation raised the values so that there was satisfactory agreement with those obtained by heat distillation. A series of experiments with pure ammonium sulfate showed that distillation by the aeration method was incomplete unless a suitable excess of strong alkali was present.

Meldrum, Melempy, and Meyers (76), studying the recovery of ammonia by aeration at different temperatures, stated that there is an advantage to be gained with respect to the time required.

A successful installation for steam distillation and its advantages have been described by Adriano (1) and also by Green (47).

There now remains only the determination of ammonia to be considered. A variety of methods is at hand. The most common procedure is to distill the ammonia into an excess of standard acid (hydrochloric or sulfuric), and titrate the remaining acid with standard alkali, the difference in the two titrations being calculated to nitrogen.

In the presence of a comparatively large volume of water and insufficient standard acid, it is possible to absorb all the ammonia without loss. Such a method was suggested by Neumann (91), who measured out slightly less than the amount of acid actually needed, and, after distillation, titrated the excess of ammonia with the same standard acid. This obviates the necessity of two standard solutions.

Along the same line is the boric acid method proposed by Winkler (145). Boric acid is an extremely weak acid and does not cause a color change with the indicators used. However, ammonia is fixed by it, and as such can be titrated directly with acid. Scales and Harrison (117), and also Spears (129), confirmed Winkler's method, and recommended bromophenol blue as an indicator. An excess of 4 per cent boric acid was used. (This represents a saturated solution of the acid.) On the other hand, Staver and Sandin (131) use a 2 per cent boric acid solution and a mixed indicator of methyl red and tetrabromophenol blue. Exhaustive experiments, performed by Sapegin and Ometov (115) on the determination of nitrogen in leather, indicated that absorption of the ammonia in 2 per cent boric acid was the most satisfactory. A mixed indicator of methylene blue and methyl red was used. Brecker (10) also used the preceding indicator and stated that methyl red alone may be used. The stability of boric acid prepared with pure water and kept in Pyrex bottles has been established by Eisner and Wagner (28).

A point to be mentioned is the presence of amines in the distillate. Erdmann (29) has suggested the presence of mono-, di-, or tri-methylamine when the compound under examination contains the groups $CH_3N=$, $CH_3NH—$ or $(CH_3)_3N=$. In a study of the Kjeldahl method, Villiers and Moreau-Talon (139) stated that the use of too energetic oxidizing agents which might break down the ammonia should be avoided. Temperature, duration of heating, and concentration also have their effect on the formation of amines. These authors distilled the ammonia into an excess of dilute hydrochloric acid, evaporated the distillate to dryness, and weighed the ammonium chloride. Chlorine was subsequently determined by either Mohr's or Volhard's method. The two results should agree, and discordant results indicate amine formation. A preliminary paper by Gortner and Hoffman (44) stated that the distillate from a Kjeldahl-Gunning digestion contains amines to the extent of 7 per cent of the nitrogen. Magnesium, calcium, barium, and strontium salts influence the amount of amines present.

A method of considerable interest is the so-called "formol titration" (46, 87, 111, 120, 123, 148), which dispenses with the distillation of ammonia. Briefly, if a neutral ammonium salt is treated with formaldehyde, hexamethylenetetramine and free acid are formed according to the following equation:

$$2(NH_4)_2SO_4 + 6HCHO \rightarrow (CH_2)_6N_4 + 2H_2SO_4 + 6H_2O$$

The liberated acid is titrated with standard alkali.

The use of Nessler's reagent gives us a colorimetric method of determining small quantities of ammonia in the distillate. It has been employed in microanalysis (60) and in the analysis of biological materials (36). Chiles (15) states that if a protective colloid such as gum arabic is employed in the nesslerization of ammonia in the presence of alkali sulfates, higher concentrations of ammonia can be determined.

Kjeldahl originally proposed the iodometric determination of the excess standard acid after distillation of the ammonia. The reaction takes place in the following manner:

$$5KI + KIO_3 + 3H_2SO_4 \rightarrow 3I_2 + 3K_2SO_4 + 3H_2O$$

$$I_2 + 2Na_2S_2O_3 \rightarrow Na_2S_4O_6 + 2NaI$$

According to Wilson and Mattingley (144), since carbon dioxide is usually present in the distillate, it is advisable to boil it off before adding the iodide–iodate solution. Owing to this sensitivity toward carbon dioxide, the method has been discarded. However, Michaelis and Maeda (79) have stated that the iodometric method applied to the microchemical determination of nitrogen is to be preferred to the acidimetric method, since the pH of the end point is ideal for the ammonia determination, and because the danger of changing the end point by carbon dioxide absorption is much less than in acidimetric determinations.

Another iodometric method, more or less general, makes use of alkaline hypobromite:

$$2NH_3 + 3NaOBr \rightarrow 3NaBr + N_2 + 3H_2O$$

$$NaOBr\ (excess) + 2KI + 2HCl \rightarrow 2KCl + NaCl + I_2 + H_2O$$

$$I_2 + 2Na_2S_2O_3 \rightarrow Na_2S_4O_6 + 2NaI$$

Willard and Cake (143) were the first to apply the above reaction to the Kjeldahl process. Various other investigators (42, 65, 103, 107, 134) have employed it, principally in the micro determination of nitrogen.

A little-used modification suggested by Sors (128) consists in exactly neutralizing the acid digest and adding a known excess of standard alkali. The ammonia is boiled off, and the remaining alkali titrated. The difference in titration represents the equivalent of ammonia that was present.

VI. APPLICATION OF THE METHOD TO THE MORE COMPLICATED COMPOUNDS

Up to this point, we have considered the nitrogen to be easily available upon oxidation. In other words, a great many natural products and pure organic nitrogen compounds have their nitrogen in basic form which is easily split off during digestion to form ammonium sulfate. There exists, however, a number of compounds whose nitrogen is present in other than a basic form, examples of which are nitrates, nitro, nitroso, and azo compounds, and compounds containing ring nitrogen. In order to rationalize the method and make it generally applicable to the many existing forms of nitrogen, a great deal of attention has been and is being given to those classes of compounds whose behavior is decidedly refractory.

In the year 1886 Jodlbauer (54) introduced the important principle of addition of phenols to the digestion mixture. These phenols, which are readily nitrated, convert the nitrogen into a form more easily reducible. For a reducing agent, Jodlbauer used zinc dust, with platinum chloride as a catalyst.

The next advance was made by Forster (37), who substituted sodium thiosulfate for zinc, and used a mixture of phenol in sulfuric acid.

Cope (18), in 1916, after an extended use, reported salicylic acid to be a very satisfactory substitute for phenols. This reagent is now generally accepted, although phenol is still used. The following equations illustrate the various phases of the conversion of a nitro compound into ammonium sulfate, the first step being the formation of nitrosalicylic acid:

$$C_6H_4(OH)COOH + NO_2R \rightarrow C_6H_3(NO_2)(OH)COOH + RH$$

After this conversion has been effected, a suitable reducing agent is added which transforms the nitrosalicylic acid into aminosalicylic acid:

$$C_6H_3(NO_2)(OH)COOH + 3H_2 \rightarrow C_6H_3(NH_2)(OH)COOH + 2H_2O$$

Now that the nitrogen has been reduced to the amino form, it can be converted easily to ammonium sulfate:

$$2C_6H_3(NH_2)(OH)COOH + 27H_2SO_4 \rightarrow (NH_4)_2SO_4 + 14CO_2 + 26SO_2 + 30H_2O$$

In addition to the two reducing agents mentioned, iron (52), zinc and iron (27), stannous chloride–tin (61), sodium hyposulfite (54, 103) ($Na_2S_2O_4$), sulfur (26), and hydriodic acid (40) have all been used.

Mention of more notable examples of compounds which are extraordinarily resistant to oxidation includes antipyrine, pyramidon, pyridine, quinoline, and isoquinoline. Many others must be subjected to special treatment before yielding their nitrogen as ammonia. It can be seen, then, that any attempt at generalization must prove more or less useless. Fleury and Levaltier (34) have studied the gases evolved during digestion, and have stated that when low values are obtained, considerable nitrogen is liberated, and some carbon monoxide.

Margosches and Vogel (70), from their work on nitro compounds, established the fact that the position of substituent groups exerted a definite influence on the digestion. They found that when an OH or RO group was in the ortho-position to the nitro group, quantitative results could be obtained. Further experiments (68) with the mononitrophenols, mono nitrobenzoic acid, and mononitrocinnamic acids showed that the sulfuric acid digestion takes place in two steps. With ortho compounds, the earlier stage is characterized by a black solution, during which time most of the nitrogen is converted to ammonium acid sulfate, the remainder being converted by the time the solution is decolorized. The para compounds give a brown solution and practically no nitrogen is converted to the ammonium salt during this time.

Further work by Margosches, Kristen, and Scheinost (71) was conducted on mono-, di-, and tri-nitrophenols, nitroanisoles, nitrophenetoles, nitrobenzoic acids, nitrobenzyl alcohols, and nitroanilines, using four modifications of the Kjeldahl method; viz., with potassium sulfate, with cupric oxide, with mercuric oxide, and without catalysts. Most of the compounds gave low results by all modifications. From the data obtained, the authors concluded (*1*) that if an hydroxyl group is ortho to the nitro group, it is usually easy to convert the nitrogen quantitatively to the ammonium salt; (*2*) that if the hydroxyl group is para to the nitro group, it is practically impossible to do so; (*3*) that a methyl group meta to the nitro group gives results close to the theoretical.

It is, therefore, necessary to resort to some means of effecting a reduction of the nitrogen of these refractory compounds to some other form that will result in complete conversion on subsequent digestion with sulfuric acid. Margosches and Kristen (72) applied Flamand and Prager's (32) modification for azo compounds. The sample is dissolved in ethyl alcohol and reduced with zinc and hydrochloric acid, followed by the ordinary digestion with sulfuric acid. The amounts of zinc, hydrochloric acid, and sulfuric acid should be increased according to the number of nitro groups present. A continuation of these studies (73) included such compounds as *m*-nitrobenzenesulfonic acid, mononitrotoluenes, and dinitrobenzenes. Nitrogen determinations (Flamand–Prager modification) were run using cupric oxide or cupric sulfate, mercuric oxide, or combinations of these as catalysts. The results were tabulated and showed that with sulfuric acid alone approximately correct results were obtained with 2,4-, and 2,6-dinitrotoluenes and with 1,2,4,6-dinitroxylene. Addition of potassium sulfate or mercuric oxide gave low results in every case, while addition of cupric oxide or cupric sulfate gave results higher than the theoretical. Low results were thought to be due to volatilization or sublimation in the digestion flask. While these modifications made possible the determination of nitrogen in some compounds hitherto classed as refractory, they cannot be considered of general application.

The preliminary reduction of osazones of the disaccharides makes it possible to use the Kjeldahl method for these compounds, although glucosazone and mannose phenylhydrazone give high results. Dorfmüller (24) stated that satisfactory results for the osazones of disaccharides and mannose phenylhydrazone are obtained by a preliminary reduction with sodium hyposulfite in sodium carbonate solution, although glucosazone gives low results. There is no reliable general method for this type of compound, and each must be considered as an individual case.

Weizmann, Yopf, and Kirzors (141) have recommended the use of fuming sulfuric acid (7 per cent sulfur trioxide) and zinc as a reducing agent for nitro compounds, and have reported good results on *o*- and *p*-nitrophenols, nitronaphthalene, and picric acid.

Another method for the reduction of nitro and azo compounds is Simek's (122) use of saturated sodium hydrosulfite solution. The sample is refluxed for 30 min., which is usually sufficient for most substances, although trinitrodihydroxybenzene requires longer. The excess sodium hydrosulfite is decomposed, the water carefully driven off, and the digestion continued in the usual manner.

The use of hydriodic acid and phosphorus (41), which has been applied to the microchemical determination, is helpful in reducing hydrazine, nitro, nitroso, and azo derivatives prior to digestion. Volatile substances, or those liberating nitrogenous decomposition products, must be reduced with hydriodic acid in a sealed tube. Diazo compounds, if first coupled with phenol to form a stable azo derivative, can be analyzed satisfactorily by this method. The use of pure dextrose (49) has been found to be helpful in determining nitrogen in azo and nitro compounds.

From the data already presented, the obvious conclusion is that there is no general method available by which all types of nitrogen can be determined. Certainly progress has been made, however, inasmuch as the nitrogen of many compounds can now be determined quantitatively through the medium of preliminary reduction, or addition of specific reagents.

VII. THE RELATION OF MICROCHEMISTRY TO ORGANIC NITROGEN

The micro Kjeldahl determination does not differ, in principle at least, from the macro method,—aside from constructional and manipulative details. It has given invaluable aid to biological and physiological research, where only small quantities of materials are available. Much of the technique was devised and many of the principles of microanalysis were laid down by Fritz Pregl, to whom necessity was the mother of invention in the matter of analyzing extremely small samples.

Numerous articles are available, dealing with modifications of the method, technique, and apparatus. Since the micro method is, as stated above, the same in principle as the macro method, the same precautions apply. Any further discussion would seem unnecessary and superfluous.

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THE PEROXIDE EFFECT IN THE ADDITION OF REAGENTS TO UNSATURATED COMPOUNDS AND IN REARRANGEMENT REACTIONS

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CONTENTS

I. INTRODUCTION

The fact that oxygen and peroxides affect the direction of addition of hydrogen bromide to allyl bromide was discovered in 1931 (53). Subse-

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quent work has demonstrated that the same agents also determine the direction of addition of various addenda to a large number of other ethylene derivatives. Because of the many papers concerned with such phenomena and the variety of interpretations offered, a critical review of the experimental work and theoretical conclusions seems desirable. Recently, J. C. Smith (139, 140, 141) has reviewed the field fully, but from a different viewpoint.

This review is based on the premise that several types of substitution and addition can proceed in solution by at least two mechanisms: a chain reaction involving free radicals and occasionally atoms, and an ionic (or molecular) reaction. The chain hypothesis has shown that several apparently different types of reaction are actually closely related, and has led to the discovery of new syntheses. Although, in most instances, details of the ionic or molecular mechanism are not yet clear, the data available permit prediction of the products of many reactions.

This review will be concerned with the addition of hydrogen bromide, mercaptans, and bisulfites to unsaturated compounds, and with certain rearrangements. The discussion will refer almost entirely to liquid-phase reactions. The important effects of oxygen and peroxides on the bromination and chlorination of hydrocarbons, acids, acid halides, and ketones, on chlorinations with sulfuryl chloride, and on carboxylation reactions will be omitted because rapid development of these fields has just begun.

II. The Addition of Halogen Acids to Unsaturated Compounds

A. NORMAL AND ABNORMAL ADDITIONS OF HALOGEN ACIDS

1. *Status of the subject in 1930*

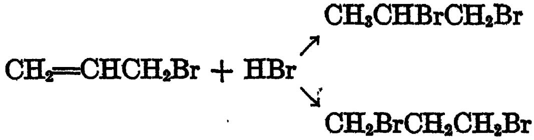
Previous to 1930, many hypotheses were current regarding the factors which controlled the direction of addition of unsymmetrical reagents to ethylene derivatives. Particular confusion existed with respect to some addition reactions which could be used to help in deciding between conflicting hypotheses. It was with the hope of reconciling some of the discordant data that an intensive investigation of the addition of halogen acids to unsymmetrically substituted ethylenes was undertaken in this laboratory.

The addition of hydrogen bromide to allyl bromide seemed of particular interest, as various workers had reported addition products ranging from nearly pure 1,2-dibromopropane to nearly pure 1,3-dibromopropane, even under supposedly identical experimental conditions. These investigators ascribed the discrepancies to variations in the temperature, the reaction time, or the concentration of hydrogen bromide, and to the presence of water or light (for references, see 53). Other factors which have been thought to direct the addition of a halogen acid to an alkene are solvents (46, 114, 117), their dielectric constants or internal pressures (44), magnetic fields (17), and previous treatment of the alkene (for references on the electromer controversy, see 77). In the vapor-phase reaction, surfaces and metal halides (15, 163, 164), oxidizing atmospheres (11), and light (10) have also been supposed to play a rôle.

It is noteworthy that most of the work on the addition of halogen acids has been carried out with hydrogen bromide, since hydrogen chloride often adds too slowly and hydrogen iodide frequently gives unstable addition products. This choice is unfortunate, because hydrogen bromide is the only halogen acid whose direction of addition to alkenes is affected by air and peroxides, and therefore the only one which can give results of doubtful significance. The following discussion will show the extent of this peroxide effect with hydrogen bromide and the absence of this effect with hydrogen chloride and hydrogen iodide.

2. The peroxide effect

The peroxide effect was discovered during an investigation of the addition of hydrogen bromide to allyl bromide (53). When these substances are allowed to react at room temperature in the dark, the reaction may take either one of two courses:



$$CH_2{=}CHCH_2Br + HBr \begin{array}{l} \nearrow CH_3CHBrCH_2Br \qquad (1) \\ \searrow CH_2BrCH_2CH_2Br \qquad (2) \end{array}$$

If the reactants are pure and freshly prepared, and if oxygen is excluded from the reaction vessel, reaction 1 takes place exclusively[2] and several days are required for substantially complete reaction. If the reaction occurs in the presence of small quantities of oxygen or if peroxides are introduced either deliberately or by use of old allyl bromide, then reaction 2 takes place almost quantitatively in a few hours. As reaction 1 is that which takes place with pure reagents in the absence of catalysts, it has been termed the *normal reaction;* reaction 2 is *abnormal.* Such a reversal of addition has been called a "peroxide effect", and it has been observed in additions of hydrogen bromide to many ethylene derivatives. In order to show that the normal and abnormal reactions take place by different mechanisms, the characteristics of the normal addition reaction will be discussed before the abnormal reaction is taken up in detail.

[2] Slight corrections (87) to the original work (53) justify this statement.

3. *The normal addition of halogen acids*

The normal product of the addition of hydrogen bromide to an alkene is uniquely and conveniently defined in terms of the addition of hydrogen chloride and hydrogen iodide, since these halogen acids are not susceptible to a peroxide effect and never add abnormally in the liquid phase. The addition of hydrogen chloride or hydrogen iodide and the normal addition of hydrogen bromide to an alkene or a halogenated alkene usually give a single product, the one which would be predicted from Markovnikov's rule (109). That is to say, the halogen of the halogen acid always becomes attached to the least hydrogenated of the two doubly bound carbon atoms. The product thus obtained is apparently the thermodynamically more stable one of the two possibilities (20).[3] The hydrogen chloride and hydrogen iodide additions in tables 1 and 2 have been carried out since the discovery of the peroxide effect. In many instances antioxidants or peroxides have been employed, or else the reaction has been carried out in a solvent with the object of altering the composition of the addition product. The addition of hydrogen chloride to propene has also been carried out in quartz apparatus in the presence of ultraviolet light (94). With three exceptions, each of these additions yields only one addition product. One exception is 1-bromopropene, which with both hydrogen chloride and hydrogen iodide gives a mixture made up of one-third 1,1-dihalide and two-thirds 1,2-dihalide, thus supplying convincing evidence that (within the limits of experimental error) these two halogen acids always add in the same way. Another mixture is that obtained by the action of hydrogen chloride on 2-pentene. As will be shown in table 4, hydrogen bromide behaves similarly to 1,2-dialkylethylenes. The third example of a mixture is the addition of hydrogen chloride to 1,3-butadiene, resulting in 75 to 80 per cent of the 1,2-addition product and 20 to 25 per cent of the 1,4-addition product. This proportion is not affected by temperature over the range −78° to 25°C. or by the presence of acetic acid. An earlier compilation (52) showed that in general the addition of hydrogen chloride or hydrogen iodide to alkenes has been reported to give only one addition product. Michael and Leighton (115) claim to have obtained a small proportion of *n*-propyl iodide by the addition of hydrogen iodide to

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[3] These statements do not hold for temperatures above 200°C. Isopropyl and propyl bromides isomerize in the liquid phase at 250–275°C. to equilibrium mixtures containing about 30 per cent of primary halide (15); isobutyl and tertiary butyl bromides are known to behave similarly. The vapor-phase addition of hydrogen chloride to isobutene (2-methylpropene) at 270°C. gives an addition product containing mostly *tert*-butyl chloride but also about 8 per cent of isobutyl chloride (112). Thus a portion of the product obtained by the addition of a halogen acid at high temperature disagrees with Markovnikov's rule. The nature of such reactions is now under investigation in this laboratory.

propene, and Ingold and Ramsden (44) claim to have obtained up to 24 per cent of primary iodide by carrying out this reaction in certain solvents. In this laboratory, repeated attempts (84) to confirm these claims have failed. It has been found that peroxides accelerate the rate of addition of hydrogen iodide (62, 84), but this effect is explained by the fact that peroxides liberate iodine from hydrogen iodide and that iodine is a catalyst for the normal addition of hydrogen iodide.

TABLE 1

The addition of hydrogen chloride to unsaturated compounds

UNSATURATED COMPOUND	FORMULA	ADDITION PRODUCT	REFERENCES
Vinyl chloride	$CH_2=CHCl$	CH_3CHCl_2	(57, 83)
Trichloroethylene	$CCl_2=CHCl$	CCl_3CH_2Cl	(74)
Propene	$CH_3CH=CH_2$	$CH_3CHClCH_3$	(15, 83, 94)
1-Bromopropene	$CH_3CH=CHBr$	$CH_3CH_2CHBrCl$ (35%) $CH_3CHClCH_2Br$ (65%)	(70, 83)
2-Bromopropene	$CH_3CBr=CH_2$	$CH_3CBrClCH_3$	(83)
1-Chloropropene	$CH_3CH=CHCl$	$CH_3CH_2CHCl_2$	(70, 83)
2-Chloropropene	$CH_3CCl=CH_2$	$CH_3CCl_2CH_3$	(83)
Allyl chloride	$CH_2ClCH=CH_2$	$CH_2ClCHClCH_3$	(83)
Isobutylene	$(CH_3)_2C=CH_2$	$(CH_3)_3CCl$	(83, 129)
2-Pentene	$CH_3CH_2CH=CHCH_3$	$CH_3CH_2CHClCH_2CH_3$ (50%) $CH_3CH_2CH_2CHClCH_3$ (50%)	(77)
Trimethylethylene	$(CH_3)_2C=CHCH_3$	$(CH_3)_2CClCH_2CH_3$	(117)
Δ^2-Pentenoic acid	$CH_3CH_2CH=CHCOOH$	$CH_3CH_2CHClCH_2COOH$	(131)
Δ^3-Pentenoic acid	$CH_3CH=CHCH_2COOH$	$CH_3CHClCH_2CH_2COOH$	(131)
Δ^4-Pentenoic acid	$CH_2=CHCH_2CH_2COOH$	$CH_3CHClCH_2CH_2COOH$	(131)
Δ^{10}-Undecenoic acid	$CH_2=CH(CH_2)_8COOH$	$CH_3CHCl(CH_2)_8COOH$	(1)
1,3-Butadiene	$CH_2=CHCH=CH_2$	$CH_3CHClCH=CH_2$ (75–80%) $CH_3CH=CHCH_2Cl$ (20–25%)	(71)
1-Hexyne	$CH\equiv C(CH_2)_3CH_3$	$CH_2=CCl(CH_2)_3CH_3$	(36)
2-Chloro-1-hexene	$CH_2=CCl(CH_2)_3CH_3$	$CH_3CCl_2(CH_2)_3CH_3$	(36)

Because it has sometimes been difficult to eliminate completely the abnormal addition of hydrogen bromide, the use of hydrogen chloride or hydrogen iodide as standards for the normal addition has been found convenient and reliable in doubtful cases (83). The normal addition products of many alkenes are listed in table 3.

Present indications are that the addition of hydrogen fluoride to alkenes also follows Markovnikov's rule (32, 102, 143). It will be indicated later that a peroxide effect with this reagent is very unlikely.

The available data justify only the following general statements as to the relation between the rate of the normal addition and the structure of the alkene. In the case of any one alkene, hydrogen chloride adds more slowly than hydrogen bromide, and the latter usually adds more slowly than hydrogen iodide. In the normal addition of hydrogen bromide (on which the most information is available), substitution of the ethylene hydrogens by alkyl or phenyl groups increases the rate of addition, whereas substitution by halogen retards the addition. Even substitution of hydrogen on an adjacent carbon atom by halogen retards addition. Some data to illustrate these statements appear in table 5.

TABLE 2

The addition of hydrogen iodide to unsaturated compounds

UNSATURATED COMPOUND	FORMULA	ADDITION PRODUCT	REFERENCES
Vinyl chloride..........	$CH_2{=}CHCl$	CH_3CHICl	(57)
Propene................	$CH_3CH{=}CH_2$	CH_3CHICH_3	(62, 84)
1-Bromopropene........	$CH_3CH{=}CHBr$	CH_3CHICH_2Br (64%) CH_3CH_2CHIBr (36%)	(84)
Allyl bromide..........	$CH_2{=}CHCH_2Br$	CH_3CHICH_2Br	(62, 84)
Allyl chloride..........	$CH_2{=}CHCH_2Cl$	CH_3CHICH_2Cl	(84)
1-Butene...............	$CH_2{=}CHCH_2CH_3$	$CH_3CHICH_2CH_3$	(62)
Trimethylethylene.....	$(CH_3)_2C{=}CHCH_3$	$(CH_3)_2CICH_2CH_3$	(117)
4,4-Dimethyl-1-pentene.	$(CH_3)_3CCH_2CH{=}CH_2$	$(CH_3)_3CCH_2CHICH_3$	(62)
Undecenoic acid........	$CH_2{=}CH(CH_2)_8$-$COOH$	$CH_3CHI(CH_2)_8COOH$	(1)
β-Iodocrotonic acid.....	$CH_3CI{=}CHCOOH$	$CH_3CI_2CH_2COOH$	(110)
Tetrolic acid...........	$CH_3C{\equiv}CCOOH$	$CH_3CI{=}CHCOOH$	(110)

Since a large portion of this review will be concerned with the mechanism of the abnormal addition of hydrogen bromide, it seems appropriate to discuss first the mechanism of normal addition. Maass and his associates have investigated the reaction of hydrogen bromide with propene and of hydrogen chloride with propene and the butenes in the absence of solvents. They find that those alkenes which (as indicated by the melting-point curves of mixtures) form 1:1 complexes with halogen acids at low temperatures react around room temperature to give addition products more easily than those which do not form complexes, that the addition is complicated by a dimerization reaction so that rate equations could not be established, and that excess halogen acid is more effective than excess alkene in accelerating the addition (19, 106, 107). No electrical conductance could be observed in these mixtures, and it was found that hydrogen chloride accelerated the addition of hydrogen bromide (106). The rate of addition of hydrogen chloride to propene increases with temperature from about −80° to +45°C. Between 45°C. and the critical temperature of the mixture (70°C.), the reaction has a negative temperature coefficient which Holder and Maass (39) have ascribed to loss of orientation or "structure" in the liquid. These liquid-phase reactions, as well as the normal addition of hydrogen bromide to allyl bromide (53), are mostly or entirely homogeneous. Above the critical temperature, at high pressure, the hydrogen chloride–propene reaction is very slow, and has a positive temperature coefficient (39). The vapor-phase additions of halogen acids to alkenes are heterogeneous, bimolecular reactions (19, 39, 99), accelerated by metal halides (15, 163). Equilibria and activation energies have been reported in a few instances (48, 99).

Kinetic investigations of the addition of halogen acids to alkenes (113, 122) in inert solvents indicate that the reaction is largely, if not entirely, of an order higher than the second. Consequently, inert solvents greatly reduce the rate of addition. That the rates are lower in ether and in dioxane than in hydrocarbon solvents is apparently a consequence of combination of the halogen acid with the solvent (122). Among oxygen-free solvents, the rate of addition increases in approximately the same order as the dielectric constants of the solvents, but in the presence of water or carboxylic acids, the reaction may be faster than in the absence of a diluent (53).

The existing data, inadequate as they are, nevertheless indicate that the conventional mechanism of normal addition, as described by Robinson (128) and Ingold (43), is an oversimplification. According to this mechanism, the proton of the halogen acid (with or without ionization) becomes attached to one of the doubly bound carbon atoms, leaving the other as a positive carbonium ion which subsequently reacts with the halide ion. Ogg (123) has pointed out that such a positive ion would be configurationally unstable and therefore inconsistent with known *trans* additions of halogen acids to some ethylene bonds. He suggests that the negative halide ion adds first to give a configurationally stable negative carbonium ion which later adds a proton. Neither mechanism is satisfactory under conditions where the reaction is of higher than the second order. Sherman, Quimby, and Sutherland (134) have discussed both a non-ionic bimolecular mechanism and a chain mechanism for the normal addition in the vapor-phase or in inert solvents. The chain mechanism is that to be described in section II, B, 5 for the abnormal reaction; reasons for rejecting it as a normal mechanism will subsequently become clear. No homogeneous bimolecular addition has yet been observed in the vapor phase, but the possibility of such a reaction cannot yet be wholly excluded for the liquid phase.

Urushibara and Sinamura (151) have suggested a different chain mechanism for the normal addition of hydrogen bromide:

$$\mathrm{RCH{=}CH_2 + H\cdot \rightarrow R\underset{\bullet}{C}HCH_3} \qquad (3)$$

$$\mathrm{R\underset{\bullet}{C}HCH_3 + HBr \rightarrow RCHBrCH_3 + H\cdot} \qquad (4)$$

Aside from the fact that this chain lacks any experimental support, it must be discarded on thermodynamic grounds. As has been mentioned elsewhere (87), reaction 4 is endothermic by about 35 kg-cal., an impossible condition for a step in a rapid chain reaction.

An explanation which seems to eliminate all of the above difficulties is that the reaction occurs, not simply between halogen acid and alkene, but between halogen acid and a halogen acid–alkene complex[4] which may contain a hydrogen bond. Such a mechanism explains why the rate depends more upon the halogen acid than upon the alkene concentration (19, 39, 106). Because the complex would be expected to be less stable at higher temperatures, the negative temperature coefficients observed in some instances (39, 111) can be accounted for. The increased reaction velocity in hydroxylic and carboxylic solvents may be due to the fact that reaction is easier when either the complex or the halogen acid is ionized.

The effects of catalysts are consistent with this idea of the mechanism of normal addition. Anhydrous ferric and aluminum chlorides are the most powerful known accelerators for the addition of hydrogen chloride and hydrogen bromide, and are particularly useful with those alkenes which otherwise react very slowly. Tests have shown that these catalysts affect only the rate and not the product of addition; in their presence only the normal addition product is obtained (83).[5] Zinc, thallous, cobaltous, and ferrous halides are moderate accelerators of the addition of hydrogen bromide to allyl bromide; cadmium, lead, stannous, cuprous, and nickelous

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[4] Coffin, Sutherland, and Maass (18a) have previously considered this and other possibilities, but have rejected them in favor of the hypothesis that reaction takes place between two molecules of complex. They consider that the latter explanation best interprets the retardation of some additions by excess alkene. This possibility must still be admitted, but in view of the fact that the authors mentioned used no solvents and could obtain no rate constants, the simpler mechanism seems preferable for the present, since it has some support from additions in solvents (113).

[5] An anomalous case is reported by Schjånberg (131), who considers that ferric chloride is a negative catalyst for the addition of hydrogen chloride to the three isomeric straight-chain pentenoic acids. That this is not a general rule for acids is shown by the fact that normal addition to Δ^{10}-undecenoic acid is accelerated by ferric chloride (139). Further work may clarify this question.

bromides (87) and platinum black (152) are weak accelerators of the same reaction. There has been little need to accelerate the addition of hydrogen iodide to alkenes, but mercuric iodide and free iodine have been found effective (84). *tert*-Butyl isocyanide accelerates the addition of hydrogen bromide to allyl bromide (53), vinyl bromide (54), and vinyl chloride (57). This effect is probably due to the formation of some kind of an ammonium salt by the reaction of the isocyanide with hydrogen bromide, since dimethylammonium bromide and tetraethylammonium bromide have been found to accelerate the addition of hydrogen bromide to allyl bromide (112). These various catalysts may alter the uncatalyzed mechanism in several ways. The metal halide (or iodine) may replace one molecule of halogen acid in the halogen acid–alkene complex; or by combining with the halogen acid, it may activate the proton so that the latter more easily forms complexes with alkenes. Whatever complex is formed, the activity of substituted ammonium halides suggests that the alkene complex may react with the halide ion of a salt more easily than with a halogen acid.

B. THE PEROXIDE EFFECT IN THE ADDITION OF HYDROGEN BROMIDE

1. Products of addition

Table 3 lists those ethylene and acetylene derivatives for which the direction of addition of hydrogen bromide is known to be affected by oxygen or peroxides. In many instances, both products indicated have been obtained in a pure condition. In the others, more or less difficulty has been encountered in completely suppressing one of the competing additions, and mixtures have been obtained, their composition depending on the experimental conditions. In the whole of table 3, there is only one instance where it is well established that the normal addition product is a mixture: 1-bromopropene gives about one-third 1,1-dihalide and two-thirds 1,2-dihalide, a result already indicated for the additions of hydrogen chloride and hydrogen iodide. In the presence of peroxides, hydrogen bromide adds to give 1,2-dibromopropane exclusively.

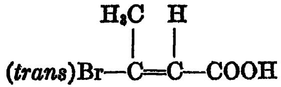
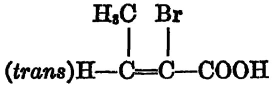
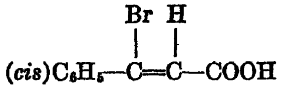
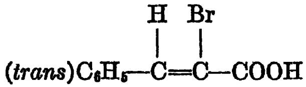
Table 3 shows that peroxides alter the direction of addition of hydrogen bromide to unsaturated hydrocarbons, halides, acids, and esters. Five examples indicate that the effect apparently applies to acetylene as well as to ethylene derivatives. In most of the compounds cited, the double bond is at the end of the carbon chain, but recent work with trimethylethylene, 2-bromo-2-butene, and 2-methyl-2-nonadecene shows that the effect is not confined to terminal double bonds.

Table 4 lists alkenes for which it has not yet been possible to reverse the addition of hydrogen bromide. This table refers only to studies carried out since the discovery of the peroxide effect, where attempts have been made to obtain more than one product. There is some uncertainty about

TAB

The peroxide effect in the direction of addition of hydrogen bromide

UNSATURATED COMPOUND	NORMAL PRODUCT	ABNORMAL PRODUCT	REFERENCES
Vinyl bromide, $CH_2=CHBr$	CH_3CHBr_2	CH_2BrCH_2Br	(54)
Vinyl chloride, $CH_2=CHCl$	$CH_3CHClBr$	CH_2BrCH_2Cl	(57)
Trichloroethylene, $CCl_2=CHCl$	CCl_2BrCH_2Cl	$CHCl_2CHClBr$	(74)
Propene, $CH_2=CHCH_3$	$CH_3CHBrCH_3$	$CH_2BrCH_2CH_3$	(15, 55, 60)
1-Chloropropene, $CHCl=CHCH_3$	$CHClBrCH_2CH_3$	$CH_2ClCHBrCH_3$	(70, 83)
2-Chloropropene, $CH_2=CClCH_3$	$CH_3CClBrCH_3$	$CH_2BrCHClCH_3$	(70)
Allyl chloride, $CH_2=CHCH_2Cl$	$CH_3CHBrCH_2Cl$	$CH_2BrCH_2CH_2Cl$	(133)
1-Bromopropene, $CHBr=CHCH_3$	$CH_2BrCHBrCH_3$ (65%) $CHBr_2CH_2CH_3$ (35%)	$CH_2BrCHBrCH_3$	(70, 83)
2-Bromopropene, $CH_2=CBrCH_3$	$CH_3CBr_2CH_3$	$CH_2BrCHBrCH_3$	(70, 83)
Allyl bromide, $CH_2=CHCH_2Br$	$CH_3CHBrCH_2Br$	$CH_2BrCH_2CH_2Br$	(53, 87, 151, 152, 154, 155)
1-Butene, $CH_2=CHCH_2CH_3$	$CH_3CHBrCH_2CH_3$	$CH_2BrCH_2CH_2CH_3$	(58)
3-Bromo-1-butene, $CH_2=CHCHBrCH_3$	$CH_3CHBrCHBrCH_3$	$CH_2BrCH_2CHBrCH_3$	(66)
2-Bromo-2-butene, $CH_3CBr=CHCH_3$	$CH_3CBr_2CH_2CH_3$	$CH_3CHBrCHBrCH_3$	(161)
Isobutylene, $(CH_3)_2C=CH_2$	$(CH_3)_3CBr$	$(CH_3)_2CHCH_2Br$	(59, 65)
1-Pentene, $CH_2=CH(CH_2)_2CH_3$	$CH_3CHBr(CH_2)_2CH_3$	$CH_2Br(CH_2)_3CH_3$	(61)
Trimethylethylene, $(CH_3)_2C=CHCH_3$	$(CH_3)_2CBrC_2H_5$	$(CH_3)_2CHCHBrCH_3$	(117, 162)
2-Bromo-1-hexene, $CH_2=CBr(CH_2)_3CH_3$	$CH_3CBr_2(CH_2)_3CH_3$	$CH_2BrCHBr(CH_2)_3CH_3$	(168)
4,4-Dimethyl-1-pentene, $CH_2=CHCH_2C(CH_3)_3$	$CH_3CHBrCH_2C(CH_3)_3$	$CH_2Br(CH_2)_2C(CH_3)_3$	(56)
1-Nonene, $CH_2=CH(CH_2)_6CH_3$	$CH_3CHBr(CH_2)_6CH_3$	$CH_2Br(CH_2)_7CH_3$	(69, 101)
1-Undecene, $CH_2=CH(CH_2)_8CH_3$	$CH_3CHBr(CH_2)_8CH_3$	$CH_2Br(CH_2)_9CH_3$	(69, 101)
1-Tridecene, $CH_2=CH(CH_2)_{10}CH_3$	$CH_3CHBr(CH_2)_{10}CH_3$	$CH_2Br(CH_2)_{11}CH_3$	(69, 101)
1-Pentadecene, $CH_2=CH(CH_2)_{12}CH_3$	$CH_3CHBr(CH_2)_{12}CH_3$	$CH_2Br(CH_2)_{13}CH_3$	(69, 101)
2-Methyl-2-nonadecene, $(CH_3)_2C=CH(CH_2)_{15}CH_3$	$(CH_3)_2CBr(CH_2)_{16}CH_3$	$(CH_3)_2CHCHBr(CH_2)_{15}CH_3$	(30)

Styrene, $C_6H_5CH{=}CH_2$	$C_6H_5CHBrCH_3$	$C_6H_5CH_2CH_2Br$	(142, 162)
Vinylacetic acid, $CH_2{=}CHCH_2COOH$	$CH_3CHBrCH_2COOH$	$CH_2BrCH_2CH_2COOH$	(104)
Allylacetic acid, $CH_2{=}CH(CH_2)_2COOH$	$CH_3CHBr(CH_2)_2COOH$	$CH_2Br(CH_2)_3COOH$	(25, 64, 104)
Δ^6-Heptenoic acid, $CH_2{=}CH(CH_2)_4COOH$	$CH_3CHBr(CH_2)_4COOH$	$CH_2Br(CH_2)_5COOH$	(25)
Δ^8-Nonenoic acid, $CH_2{=}CH(CH_2)_6COOH$	$CH_3CHBr(CH_2)_6COOH$	$CH_2Br(CH_2)_7COOH$	(25)
Δ^{10}-Undecenoic acid, $CH_2{=}CH(CH_2)_8COOH$	$CH_3CHBr(CH_2)_8COOH$	$CH_2Br(CH_2)_9COOH$	(4, 35, 156)
Ethyl Δ^{10}-undecenoate, $CH_2{=}CH(CH_2)_8COOC_2H_5$	$CH_3CHBr(CH_2)_8COOC_2H_5$	$CH_2Br(CH_2)_9COOC_2H_5$	(5)
Δ^{10}-Undecenyl acetate, $CH_3COO(CH_2)_9CH{=}CH_2$	$CH_3COO(CH_2)_9CHBrCH_3$	$CH_3COO(CH_2)_{10}CH_2Br$	(5)
Δ^3-Pentenoic acid,* $CH_3CH{=}CHCH_2COOH$	$CH_3CHBr(CH_2)_2COOH$	$CH_3CH_2CHBrCH_2COOH$	(12, 131)
Propyne, $CH{\equiv}CCH_3$	$CH_3CBr_2CH_3$	$CH_2BrCHBrCH_3$	(63)
1-Hexyne, $CH{\equiv}C(CH_2)_3CH_3$	$CH_2{=}CBr(CH_2)_3CH_3$	$CHBr{=}CH(CH_2)_3CH_3$	(168)
Δ^{10}-Undecynoic acid, $CH{\equiv}C(CH_2)_8COOH$	$CH_2{=}CBr(CH_2)_8COOH$	$CHBr{=}CH(CH_2)_8COOH$	(35)
Tetrolic acid,† $CH_3C{\equiv}CCOOH$	 (*trans*)$Br{-}\overset{H_3C}{C}{=}\overset{H}{C}{-}COOH$	 (*trans*)$H{-}\overset{H_3C}{C}{=}\overset{Br}{C}{-}COOH$	(116)
Phenylpropiolic acid,† $C_6H_5C{\equiv}CCOOH$	 (*cis*)$C_6H_5{-}\overset{Br}{C}{=}\overset{H}{C}{-}COOH$	 (*trans*)$C_6H_5{-}\overset{H}{C}{=}\overset{Br}{C}{-}COOH$	(116)

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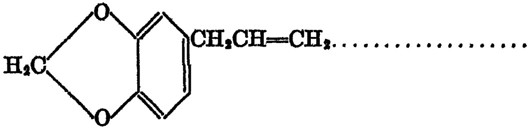
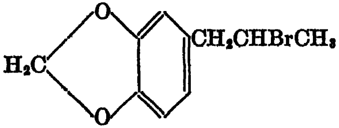
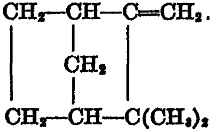
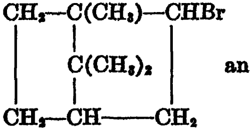
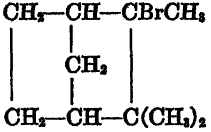
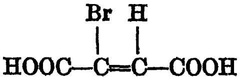
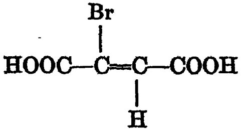
* The composition of the normal addition product is based on work with hydrogen chloride. The addition of hydrogen bromide (without special precaution to exclude oxygen) gave 8 per cent of the product listed as abnormal and 92 per cent of the normal product. The proportion of β-bromovaleric acid might be increased above 8 per cent under proper conditions.

† These acids are included here on the basis of analogies to be discussed in the section on the effects of solvents. The reference cited does not mention the addition of peroxides or antioxidants, or exclusion of air, but reports differences in the addition products which depend on the solvent employed. Grigorieff (29) investigated the addition of hydrogen bromide to tetrolic acid in the absence of solvents. In the presence of antioxidants, the primary product was a β-bromocrotonic acid of melting point 54°C.; in the presence of peroxides, a β-bromocrotonic acid of melting point 94°C. Both isomers on further reaction with hydrogen bromide gave only β,β-dibromobutyric acid. These reactions require further investigation.

TABLE 4

Unsaturated compounds which do not exhibit a peroxide effect with hydrogen bromide

UNSATURATED COMPOUND	ADDITION PRODUCT	REFERENCES
Section A:		
2-Pentene, $CH_3CH{=}CHC_2H_5$	Approximately 50 per cent of each of the two possible addition products	(77)
Δ^9-Undecenoic acid, $CH_3CH{=}CH(CH_2)_7COOH$		(2)
Δ^9-Undecenamide, $CH_3CH{=}CH(CH_2)_7CONH_2$		(2)
9-Undecene-1-ol, $CH_3CH{=}CH(CH_2)_8OH$		(2)
Section B:		
Δ^{10}-Undecenol, $CH_2{=}CH(CH_2)_9OH$	$CH_3CHBr(CH_2)_9OH$	(5)
Section C:		
Propenylbenzene, $C_6H_5CH{=}CHCH_3$	$C_6H_5CHBrC_2H_5$	(98)
Safrole, 		(103)
1-Bromo-2-butene,* $CH_2BrCH{=}CHCH_3$	$CH_3CHBrCHBrCH_3$ (22%) $CH_2BrCH_2CHBrCH_3$ (78%)	(66)
1-Bromo-1-hexene, $CHBr{=}CH(CH_2)_3CH_3$	$CH_2BrCHBr(CH_2)_3CH_3$	(168)
Camphene, 	 and 	(38)
Section D:		
Crotonic acid, $CH_3CH{=}CHCOOH$	$CH_3CHBrCH_2COOH$	(30, 116, 162)
Ethyl crotonate, $CH_3CH{=}CHCOOC_2H_5$	$CH_3CHBrCH_2COOC_2H_5$	(162)
Acrylic acid, $CH_2{=}CHCOOH$	CH_2BrCH_2COOH	(95)
Methyl methacrylate, $CH_2{=}C(CH_3)COOCH_3$	$CH_2BrCH(CH_3)COOCH_3$	(126)

β-Bromocrotonic acid, $CH_3CBr{=}CHCOOH$	$CH_3CBr_2CH_2COOH$	(29)
Cinnamic acid, $C_6H_5CH{=}CHCOOH$	$C_6H_5CHBrCH_2COOH$	(116)
Bromomaleic acid,  $HOOC{-}\overset{\overset{\displaystyle Br}{\vert}}{C}{=}\overset{\overset{\displaystyle H}{\vert}}{C}{-}COOH$	meso and racemic $HOOCCHBrCHBrCOOH$	(95, 93)
Bromofumaric acid,  $HOOC{-}\overset{\overset{\displaystyle Br}{\vert}}{C}{=}\underset{\underset{\displaystyle H}{\vert}}{C}{-}COOH$		

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* This unsaturated compound rearranges under the influence of hydrogen bromide; *cf.* V, A.

placing compounds in this table, because a past failure to obtain a second addition product does not prove that future attempts will likewise be failures. For example, early attempts to reverse the addition of hydrogen bromide to styrene failed, but improved technique gave up to 80 per cent of the abnormal product (162).

It seems well established that peroxides do not affect the direction of addition of hydrogen bromide to the ethylene derivatives in section A of table 4. Here the normal addition products are 50–50 mixtures, and complete reversal of the addition gives the same result. Note that, as far as directing tendency is concerned, methyl has the same effect as ethyl or a long-chain alkyl with a substituent on the end.[6] Thus there are few examples of a peroxide effect upon non-terminal double bonds. It should be pointed out here that symmetrically substituted ethylenes, e.g., 2-butene, can give only one structurally distinct addition product, but this fact does not preclude the possibility that the product in question can be formed by two mechanisms.

Alkenes containing a group which inhibits abnormal addition may fail to give an abnormal product. The only known example of such a compound is Δ^{10}-undecenol (in section B of table 4); primary alcohol groups are weak inhibitors of abnormal addition. Until more data on such compounds are available, it should be concluded that the presence of an inhibiting group in an alkene makes abnormal addition less likely but not impossible.

In section C are listed some doubtful cases in which attempts to obtain two addition products have been made. It is probably because the best experimental procedures have not yet been employed that the second products have not been detected. In the opinion of the reviewers, propenylbenzene, safrole, and (if isomerization[7] can be retarded) 1-bromo-2-butene should give two addition products. Because of the behavior of 1-bromopropene, no comment is made on additions to 1-bromohexene. Camphene is a special case, because its predicted abnormal addition product is unknown and because acids rearrange its carbon skeleton.

Section D (table 4) consists of α, β-unsaturated acids and esters. Even when an improved technique was used, crotonic acid and crotonic ester gave only β-bromobutyric acid or ester, with no indication of α-brominated derivatives. Attempts to obtain a second addition product from the other acids listed have failed, but the improved technique has not yet been

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[6] The case of Δ^3-pentenoic acid, listed in table 3, is not an exception to this statement, since the carboxyl group is separated from the double bond by only one methylene group. Normal addition gives one product.

[7] This rearrangement, together with the addition of hydrogen bromide to butadiene, will be considered in the section on rearrangements (V, A).

employed. Explanations will be considered in the section on the mechanism of the abnormal addition. A fact pertinent to bromomaleic and bromofumaric acids is that 1,1-dibromosuccinic acid is unknown and may be incapable of existence. Although no instance is known of a peroxide effect on an acid containing an α,β-double bond, there are indications of such an effect on the α,β-triple bonds of tetrolic and phenylpropiolic acids (table 3).

The present section has thus far dealt only with the effects of oxygen and peroxides on the direction of addition of hydrogen bromide in liquid-phase reactions. The data on vapor-phase reactions are contradictory but of interest because, about ten years before the peroxide effect was reported in the scientific literature, suggestions of such an effect in the vapor phase appeared in Bauer's patents. He claimed that the addition of hydrogen chloride, bromide, or iodide to acetylene and vinyl bromide, in the presence of an oxidizing atmosphere containing oxygen, ozone, chlorine, or nitrogen oxides (11), or in the presence of light (10), gives ethylene halides rather than ethylidene halides. Kharasch and Walker (97) have found that oxygen accelerates the addition of hydrogen bromide to propene, 2-pentene, and butadiene, and Kistiakowsky and Stauffer (99) mention a similar effect in the addition of "halogen acids" to "isobutene." Brouwer and Wibaut (15) state that oxygen does not affect the direction of addition of either hydrogen bromide or hydrogen chloride to propene. Vapor-phase reactions need further investigation.

2. Rates of addition

A consideration of the rates of some normal and abnormal addition reactions will be of assistance in showing that the two reactions are independent and competing, and that the susceptibility of an alkene to the peroxide effect is directly related to the rate of its normal addition reaction. No quantitative data are available, but table 5 has been compiled from experiments which have been carried out in the same laboratory under comparable conditions: that is, at room temperature, with about 1.5 moles of hydrogen bromide per mole of alkene, and (except as noted) in the absence of solvents.

The alkenes are listed approximately in order of increasing rate of normal reaction with hydrogen bromide and of decreasing susceptibility to the peroxide effect. When the normal addition is extremely slow (section A), traces of oxygen and peroxides can exert a maximum effect; unless the normal addition is specifically catalyzed, abnormal addition predominates, even in the presence of an antioxidant. When the normal addition is somewhat faster (section B), it can outrun the abnormal addition only when the latter is inhibited by an antioxidant. With allyl bromide (section C), exclusion of air and ordinary purification of materials permit the normal to exclude the abnormal addition, although the latter occurs in the presence of air. With the alkenes in section D, air alone is ordinarily insufficient to influence the course of the reaction and definite admixture of peroxides is required to prevent fairly rapid formation of the normal addition product. In section E, the normal addition is so fast that it must be retarded by the use of a solvent in order to obtain the abnormal product. Even so, about 20 per cent normal addition occurs.

TABLE 5

Rate of addition of hydrogen bromide to unsaturated compounds

UNSATURATED COMPOUND	NORMAL ADDITION			ABNORMAL ADDITION			REFERENCES
	Yield*	Time	Conditions†	Yield*	Time	Conditions†	
	per cent	*hours*		*per cent*	*hours*		
Section A:							
Trichloroethylene	0	1440	(1)	27	24	(3)	(74)
1-Bromopropene	Very little		(1)	84	3	(3)	(70)
1-Chloropropene	25	850	(1)	21	1	(3)	(70)
Section B:							
Vinyl bromide	79	1632	(1)	70	31	(2)	(54)
Vinyl chloride	59	336	(1)	76	48	(2)	(57)
Section C:							
Allyl bromide	95	240	(1)	100	<16	(2)	(53)
Section D:							
2-Bromopropene	92	27	(1)	80	5	(2)	(70)
2-Chloropropene	70	40	(1)	>86	7	(2)	(70)
Propylene	70	3	(1)	41	0.25	(3)	(55)
Isobutylene	100	1	(2)	‡		(3)	(59)
Section E:							
2-Bromo-2-butene	55	2	(1)	Faster		(4)	(161)
Trimethylethylene	‡		(1)	‡		(4)	(162)
Styrene	‡		(2)	‡		(4)	(162)

* When a 90 to 100 per cent yield was obtained, the time given represents only an upper limit to the period required for substantially complete reaction.

† Conditions: (1) air absent, antioxidant present; (2) air present; (3) peroxide present; (4) dilute pentane solution with a peroxide present (otherwise no solvent was employed). All reactions were carried out near room temperature, usually in sealed tubes.

‡ Reaction appeared to occur as rapidly as hydrogen bromide was added.

These observations are all consistent with the view that the two types of addition are independent but competing; the structure of the alkene and the conditions of addition determine the product which predominates. This view is supported by the fact that each alkene in sections B and C has yielded many different mixtures of the two possible products at rates intermediate between those of the independent reactions. Similar examples will be indicated in the section on the influence of experimental conditions.[8]

Evidence showing how the rate of abnormal addition varies with the structure of the alkene is unsatisfactory, but indications are that the alkenes in section A, particularly trichloroethylene, are also distinguished by slow abnormal additions.

3. Catalysts of abnormal addition

Of the materials which catalyze the abnormal addition, the first ones to be detected, and the most important on account of their wide prevalence, are oxygen and peroxides. Most alkenes, on standing, react with air to form materials which give the familiar test for peroxides; that is, they give an intense red color when shaken with an aqueous solution containing ferrous and thiocyanate ions.[9] The ability of these natural peroxides to cause abnormal addition depends on the extent of their formation and on the rate of the normal addition. For allyl bromide, where the most data are available and where the rate of the normal addition is moderate, the quantities of oxygen or peroxide required are small. Urushibara and Takebayashi (154) state that 1.5 cc. of oxygen per 24.2 g. of allyl bromide (0.03 mole per cent) is sufficient to give a product containing 96 per cent of 1,3-dibromopropane (abnormal). Because about three times as much

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[8] Such observations disagree with the opinion of Urushibara and Takebayashi (151) that the normal and abnormal additions so cancel each other that only one can proceed at a time. This view is based on a chain mechanism for normal addition which the reviewers have questioned in section II, A, 3. Assumptions about the effect of one mechanism on the other seem unnecessary, because any rate of reaction or any addition product thus far recorded may be accounted for on the following basis: The abnormal addition may have an induction period (140), proceed very rapidly for a time through the action of peroxides, and then more slowly through the effect of oxygen.

[9] Urushibara and Takebayashi (153) state that when oxygen was passed through allyl bromide in the dark, no peroxides were formed in one month, whereas a strong test could be obtained after the bromide was kept for a few hours in diffused light. However, Urushibara and Sinamura (151) record that when oxygen and hydrogen bromide together were passed through allyl bromide in the dark, considerable oxidation took place, as indicated by formation of water, the liberation of heat, the temporary formation of bromine, and the development of a peroxide test. A good yield of 1,3-dibromopropane was obtained. Such experiments have never been carried out in this laboratory, but it has been repeatedly observed that, when allyl bromide is stored in the dark in a bottle containing air, and only intermittently exposed to light for the purpose of withdrawing samples, a weak peroxide test can be obtained after a few days and a very strong test after a few weeks. The 1- and 2-chloro- and bromo-propenes, as well as styrene, form peroxides more rapidly.

peroxide (formed spontaneously and determined by its ability to oxidize iodide ion) was required to produce a similar effect, they suggest that molecular oxygen, rather than organic peroxides, is responsible for the peroxide effect, and that peroxides function by liberating this gas. The reviewers know of no observations that alkene peroxides liberate oxygen.

Added peroxides are quite as effective as those formed spontaneously in the alkene. Among those which have been successfully used are benzoyl peroxide, lauroyl peroxide, perbenzoic acid, and ascaridole (natural menthene peroxide). The quantities employed have usually been of the order of 1 mole per cent.

Smith has observed the rate of addition of hydrogen bromide to undecenoic acid in various solvents and under various atmospheres. He found that there is an induction period in the abnormal addition when air or benzoyl peroxide is the catalyst, but not when perbenzoic acid, which liberates bromine immediately, is used. In experiments with purified materials in fairly concentrated solution, air, but not perbenzoic acid, gave an abnormal addition reaction. Smith concludes that oxygen is essential for the abnormal reaction and that peroxides serve as subsidiary catalysts (35, 140). Observations in this laboratory (53, 55, 61, 63, 70) show that both benzoyl peroxide and ascaridole can serve as catalysts for the abnormal reaction in the absence of air, but that the rate and extent of abnormal addition are often more unpredictable with peroxides[10], particularly perbenzoic acid, than with oxygen.

A simple explanation of these results, as well as those of Urushibara, Takebayashi, and Smith, is as follows: Either oxygen or peroxides can serve as catalyst for the abnormal addition reaction by reacting with hydrogen bromide. If the peroxide reacts rapidly, as do ascaridole and perbenzoic acid, the catalyst is quickly destroyed before much abnormal addition has taken place. On the other hand, benzoyl peroxide[11] and oxygen react very slowly with hydrogen bromide under the usual experimental conditions, and thus exert a catalytic effect over a comparatively long period. The observations of other workers that peroxides may be less effective than oxygen in catalyzing abnormal addition are not questioned; nevertheless their conclusion that molecular oxygen is necessary seems to the reviewers to be unjustified.

Other gases than oxygen, and other oxidizing agents than peroxides, have been investigated for a possible effect on the abnormal addition. Nitrogen, hydrogen, nitric oxide, and nitrogen dioxide were tried with

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[10] With trichloroethylene (74) benzoyl peroxide caused abnormal addition when air did not.

[11] This statement applies particularly to experiments without solvents, when the benzoyl peroxide dissolves slowly.

allyl bromide and found to be without effect (53). Neither lead dioxide nor bromine (in the dark and in the absence of air) had any effect on the addition to allyl bromide (53), nor did *N*-bromobenzamide and iodine affect addition to propene (111). Smith, however, working with diffused light and in a hydrogen atmosphere, found that intermittent additions of bromine caused an abnormal addition to undecenoic acid in carbon tetrachloride solution (140). Harris and Smith (35) report that α-heptenylheptaldehyde and 10,11-epoxyundecanoic acid are catalysts for the abnormal addition of hydrogen bromide to undecenoic acid in the presence of air, but have only a small effect in its absence. In the faster addition of hydrogen bromide to propene (without a solvent), both propylene oxide and propionaldehyde, when peroxide-free, were ineffective even in the presence of air (111). Therefore such catalysts probably function because they, or impurities which they contain, are oxidized by air to peroxides.[12]

Finely divided iron, cobalt, and nickel are strong catalysts for the abnormal addition of hydrogen bromide to allyl bromide and undecenoic acid; these reactions will be considered later.

4. Inhibitors of abnormal addition

It has been found that small proportions, usually 1 to 5 mole per cent, of certain substances prevent abnormal addition when this reaction would otherwise predominate. These inhibitors are commonly called antioxidants because they overcome the effect of oxygen, but many of them are not inhibitors of autoöxidation reactions. Table 6 summarizes some of the available information on inhibitors of abnormal addition, and permits rough evaluation of their effectiveness. The alkenes in section A are those which put antioxidants to the most severe test. For these compounds no antioxidant has been found which completely prevents abnormal addition, except in the presence of a catalyst for the normal reaction. In section B, the inhibitors are effective for propene only when this compound is carefully and freshly purified and when a clean vacuum line is used. The other sections bring out further differences in the effectiveness of antioxidants, and it can be concluded that compounds with sulfhydryl groups are the best inhibitors; some phenols and aromatic amines are less effective. It should be noted that the effectiveness of the inhibiting substances is related to their solubility. This fact may account for the moderate efficacy of diphenylamine (the hydrobromide of which is rather soluble

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[12] Note added August 8, 1940: This conclusion is supported by the paper of M. Takebayashi (Bull. Chem. Soc. Japan **15**, 116 (1940)). He found that the effect of aldehydes on the addition of hydrogen bromide to undecenoic acid depended on the peroxide content of the aldehydes.

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Inhibitors of abnormal additions

REAGENTS AND CONDITIONS	EFFECTIVE	PARTIALLY EFFECTIVE	INEFFECTIVE
Section A: 1-Halopropenes; air absent (70)		Thiophenol Ethyl mercaptan	Diphenylamine Catechol
Section B: Various alkenes in hydrocarbon solvents; air absent (a) $CH_2{=}CH(CH_2)_nCOOH$ (25) (b) Butylacetylene, 2-bromo-1-hexene (168) (c) Propene (113)		Diphenylamine Hydroquinone + ferrous bromide* *p*-Thiocresol Thiophenol 4-*tert*-Amylphenol	
Section C: Trimethylethylene in ether solution at 0°C.; air present (117)	Hydroquinone	Diphenylamine	
Section D: Allyl bromide and undecenoic acid in the presence of finely divided metals; air absent			
(a) Undecenoic acid in toluene solution (158), *or* allyl bromide (157); nickel	Catechol Hydroquinone	Diphenylamine	
(b) Allyl bromide; iron (87)	Thiophenol Catechol Cuprous bromide, stannous bromide	Resorcinol Phenol Diphenylamine Ferrous bromide,* nickelous bromide, cobaltous bromide*	

Section E:			
Vinyl halides; air absent (54, 57)	Thiocresol (freshly distilled) Thiophenol Diphenylamine Phenyl-β-naphthylamine Dimethylaniline Nitric oxide	Thiocresol (partially oxidized) *tert*-Butyl isocyanide*†	Manganous chloride Ammonium bromide Diphenyl ether Potassium cyanide
Section F:			
Allyl bromide; air present (53, 87)	Diphenylamine Hydroquinone Phenyl-β-naphthylamine Dimethylaniline Resorcinol		Diphenyl ether Ammonium bromide Potassium cyanide

* A part of the inhibitory effect of these substances on abnormal addition may be due to their ability to catalyze the normal addition.

† Effectiveness depends on peroxide content of vinyl halide.

in the reaction mixtures), for the fact that catechol is often better than hydroquinone, and for the differences between some of the metal halides.

Ethanol has been found to inhibit abnormal addition to Δ^{10}-undecenoic acid (35) and to trimethylethylene (162). In a later section it will be shown that this inhibiting effect decreases at lower temperatures.

5. The bromine-atom mechanism of abnormal addition

At this point it seems desirable to correlate the data so far presented by means of a mechanism for the abnormal addition. Since this reaction can be caused by relatively small quantities of oxygen and peroxides and inhibited by equally small quantities of antioxidants, it is established that the abnormal addition is a chain reaction. In choosing a mechanism for the reaction, it must be explained how oxygen and peroxides start reaction chains, how the chains give the abnormal addition product, and why hydrogen bromide is the only halogen acid capable of reacting through such a chain. In order to meet the last requirement, it seems necessary that the oxygen or peroxides function through the hydrogen bromide rather than through the alkene; otherwise it would be difficult to explain why the addition of other unsymmetrical reagents is not also reversed by these reagents. If oxygen or peroxides attack hydrogen bromide, bromine should result; but molecular bromine has no effect on the reaction in the dark. It has therefore been suggested that the slow oxidation of hydrogen bromide in dilute solution gives bromine atoms. In adding to a double bond, these atoms need not attack the same doubly bound carbon atom which would be attacked by the proton in the normal addition. Although oxidation of hydrogen bromide might conceivably give positive bromine ions, and although these ions should add abnormally to double bonds, formulation of the mechanism of the abnormal addition in terms of bromine atoms (70)[13] is preferred, because more energy would be required to separate charged particles in non-polar solvents. According to this mechanism, the reaction should proceed as follows:

$$\mathrm{HBr} + \mathrm{O_2} \xrightarrow{\text{(alkene)}} \mathrm{H{-}O{-}O^{\bullet}} + \mathrm{Br^{\bullet}} \tag{5}$$

$$\mathrm{RCH{=}CH_2} + \mathrm{Br^{\bullet}} \rightarrow \mathrm{R\underset{\bullet}{C}HCH_2Br} \tag{6}$$

$$\mathrm{R\underset{\bullet}{C}HCH_2Br} + \mathrm{HBr} \rightarrow \mathrm{RCH_2CH_2Br} + \mathrm{Br^{\bullet}} \tag{7}$$

The individual steps suggested will next be discussed.

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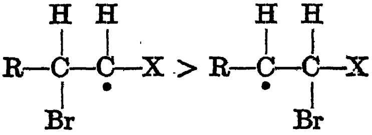
[13] The suggestion that the abnormal addition is a chain mechanism involving bromine atoms was made simultaneously and independently, but without details, by Hey and Waters (37). Previously, Burkhardt (16) had suggested that free radicals might account for the abnormal addition of thiophenol to styrene; *cf.* section III, B.

The oxidation of hydrogen bromide by oxygen is ordinarily slow, but Urushibara and Sinamura have shown that in the presence of an alkene such as allyl bromide, peroxides are very rapidly formed (151). These organic peroxides react slowly with hydrogen bromide. The same authors also showed that the interaction of hydrogen bromide, oxygen, and stilbene gives stilbene dibromide, thus proving the oxidation of hydrogen bromide. Similarly, the abnormal addition of hydrogen bromide to allyl bromide is accompanied by the formation of small amounts of a high-boiling liquid which is apparently 1,2,3-tribromopropane (94, 151). The essential feature of reaction 5 is that at least a small portion of the bromine formed must be liberated in the atomic state. This requirement is consistent with the fact that those peroxides which react more slowly with hydrogen bromide are usually more effective; it also agrees with the observation of Smith (140) that bromine is a catalyst for the addition of hydrogen bromide in diffused light. The fate of the $HO_2^\bullet$ radical is unimportant. It may react with hydrogen bromide to give another bromine atom and hydrogen peroxide, or it may combine with alkene.

If reaction 5 is assumed, reaction 6 can follow very easily. In the normal addition to the type of alkene chosen as an example, the proton becomes attached to the terminal carbon atom, showing that this atom is the relatively negative carbon atom of the double bond. In abnormal addition the bromine atom becomes attached to this terminal carbon atom. It has already been suggested (70) that the oxidizing properties of the bromine atom cause it to attack the carbon atom with the higher electron density. This explanation is simple and plausible, but the following one has additional advantages: The point of attack by the bromine atom is little affected by the polarity of the double bond, but depends upon the relative stability of the two bromoalkyl radicals which may be formed. If the directions of all additions by the chain mechanism are to be explained on this basis, the following orders of decreasing stabilities of free radicals (each formed by the addition of a bromine atom to a double bond) are required:

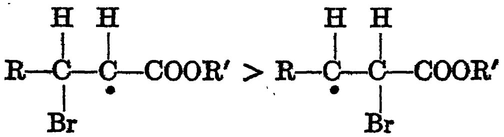
Radicals from hydrocarbons: tertiary > secondary > primary

Radicals from vinyl-type halides:



$$R—\underset{Br}{\overset{H}{C}}—\underset{\bullet}{\overset{H}{C}}—X > R—\underset{\bullet}{\overset{H}{C}}—\underset{Br}{\overset{H}{C}}—X$$

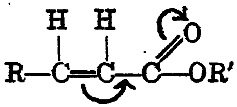
Radicals from acids, esters:



$$R—\underset{Br}{\overset{H}{C}}—\underset{\bullet}{\overset{H}{C}}—COOR' > R—\underset{\bullet}{\overset{H}{C}}—\underset{Br}{\overset{H}{C}}—COOR'$$

Radical stability in this discussion is intended in the sense of higher heat of formation; no reference to the mean life of the radical is implied. If these relative stabilities can be proved correct, then the hypothesis of radical stability explains why addition of hydrogen bromide by the abnormal rather than the normal mechanism gives complete reversal of addition with hydrocarbons, only partial reversal with 1-bromopropene (to give exclusively 1,2-dibromopropane), and no change when the ethylene bond is conjugated with the carboxyl group.

This hypothesis suggests that the addition of hydrogen bromide to such conjugated double bonds may take place through two mechanisms to give only one product. Addition by the normal mechanism must be fast as compared with addition by the chain mechanism, in order to agree with the following qualitative rate indications. The rate of addition of hydrogen bromide to crotonic acid and its ethyl ester is unaffected by peroxides, even when the normal addition is retarded by the use of an inert solvent (162). These conclusions as to the relative rates of addition by the two mechanisms are in agreement with experiments (to be described in section V, C) on the relative rates of isomerization of maleic acid to fumaric acid by corresponding mechanisms. Smith (141) has suggested that since ethylene bonds conjugated with carboxyl groups should be represented by the formula



$$\mathrm{R{-}\overset{\overset{H}{|}}{C}{=}\overset{\overset{H}{|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}OR'}$$

and that since there is no "accumulation" of electrons on the α-carbon atom, there is no tendency for the bromine atom to attack this position or for abnormal addition to occur. This explanation is in good agreement with the qualitative observations on the rate of addition of hydrogen bromide, but not with the isomerization studies mentioned. In the opinion of the writers, no explanation yet proposed for the absence of abnormal addition to conjugated systems is wholly satisfactory.

In order to obtain the addition product from the free radical formed in reaction 6, reaction 7 is necessary. This latter step regenerates a bromine atom, so that the chain reactions (6 and 7) can continue indefinitely. The inhibition of the abnormal reaction by small quantities of antioxidants is excellent evidence that this reaction is of the chain type. The small amounts of antioxidants usually needed to inhibit and the small amounts of peroxides necessary to cause abnormal addition indicate that the chains must be very long. If 0.03 mole per cent of oxygen causes nearly complete abnormal addition to allyl bromide (154), and if each molecule of oxygen generates four bromine atoms by oxidizing hydrogen bromide, then the average chain length is at least 1000. If the efficiency in generating bromine atoms is low, as seems likely, then the chains must be much longer. These chain lengths, together with the observed high velocity of the abnormal addition and the known instability of aliphatic free radicals, indicate that both steps in the chain reaction must take place very rapidly and with little or no activation energy. The inhibition of the reaction by antioxidants suggests that these function by reacting with bromine atoms. It is also possible, as originally suggested (53), that antioxidants to some extent destroy organic peroxides. Other observations on the abnormal addition are consistent with the chain mechanism suggested. The abnormal reaction is retarded by glass wool (139), although apparently not by coarser packing (155). When non-polar solvents are used, the absence of a large dilution effect (113) shows that the abnormal reaction cannot be of second or third order.

TABLE 7

*Heats of addition of halogen acids to double bonds**

STEP IN CHAIN REACTION	ΔH (IN KILOGRAM-CALORIES PER MOLE)			
	X = F	X = Cl	X = Br	X = I
(6) $RCH{=}CH_2 + X^{\bullet} \rightarrow R\underset{\bullet}{C}HCH_2X$.........	64; 66	27; 25	13	−1; +4
(7) $R\underset{\bullet}{C}HCH_2X + HX \rightarrow RCH_2CH_2X + X^{\bullet}$.	−60	−15	0	16

* When two values are given for ΔH, the first is based on the bond-energy estimates of Sherman and Ewell (31), the second on the estimates of Pauling (124). One value for ΔH indicates that both sources give the same result.

It will now be indicated why hydrogen bromide is the only halogen acid capable of giving an abnormal addition. The exposition assumes that a rapid chain reaction is impossible when any step is appreciably endothermic. Table 7 gives estimates of the heats evolved in reactions 6 and 7 for various halogen acids; it is assumed that ΔH for each reaction is simply the difference between the energies of the bonds formed and the energies of the bonds broken. The heats indicated are only approximate, for the bond energies are none too well established for the molecules to which they are meant to apply and are still less reliable when applied to free radicals.[14] Table 7 shows that reaction 6 for hydrogen bromide is definitely exothermic and that the heat of reaction 7 is very close to zero. However, the addition

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[14] Actually, the activation energy rather than the ΔH will determine the probability of reaction. Because long chains occur in some additions, it is assumed here that the activation energy is small when ΔH is positive or zero.

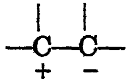
of hydrogen chloride by the same mechanism encounters difficulty in two places, reactions 5 and 7. Since the oxidation of hydrogen bromide is ordinarily slow (reaction 5), the oxidation of hydrogen chloride is probably slower, possibly negligible. In reaction 7 the carbon–chlorine bond formed is weaker than the hydrogen–chlorine bond broken; the reaction is endothermic by about 15 kg-cal. per mole, and unlikely to occur rapidly enough to support long chains at ordinary temperatures. Both of these difficulties apply also to hydrogen fluoride and to most other acids. Attempts to reverse the direction of addition of sulfuric acid to propene, 1-pentene, and 2-pentene have failed (14).

In the addition of hydrogen iodide, reactions 5 and 7 should proceed easily, but reaction 6 may not. Another difficulty with the addition of hydrogen iodide is that the normal addition is ordinarily rapid and is further catalyzed by molecular iodine. Any reagent which generates iodine atoms must necessarily generate also the catalyst for the normal addition. Still another possibility is that iodine, since it does not add readily to alkenes, may accumulate in the reaction mixture and inhibit any possible abnormal addition of hydrogen iodide by an iodine-atom mechanism. According to the chain mechanism proposed, the unsymmetrical reagents, HX, which can add by a chain mechanism are restricted to narrow limits. The requisites are as follows: the radical (or atom) X must be able to break a carbon–carbon double bond and add to one carbon atom; the free radical formed must be able to take a hydrogen atom away from HX to regenerate another X radical. It will be shown later that this mechanism can also be applied to additions of mercaptans and bisulfites.

The next abnormal additions to be considered are those occurring when air and peroxides have been excluded from reaction mixtures (135, 136) and when antioxidants have been added (25, 70, 117). The discussion of antioxidants showed that these substances exert effects ranging from complete to barely perceptible repression of the abnormal addition. Since different antioxidants have variable effects under the same experimental conditions, the occasional failure of the best antioxidants and the more frequent failure of inferior inhibitors indicate only that the proportions used or the inhibiting qualities of the compounds were inadequate; they do not indicate a difference in the nature of the abnormal reaction. It is thus proved for the weaker antioxidants, and inferred for the rest, that only a small proportion of the collisions of a bromine atom with an antioxidant molecule are effective in terminating chains. The smaller this proportion, the greater must be the chain lengths and the fewer the number of bromine atoms necessary to cause abnormal addition. Since there is no basis for estimating an upper limit on chain lengths, it can be argued that traces of peroxides and oxygen which would defy elimination or detection by any known method may be wholly responsible for all abnormal addition reactions. On the other hand, infinitesimal quantities of atoms or radicals may appear spontaneously in the solution with the result that chains are initiated. The dissociation of hydrogen bromide into atoms would require 87 kg-cal. per mole (31, 124), but the dissociation of a carbon–bromine bond in an alkyl halide requires on the average only 50 to 60 kg-cal. Such a dissociation might initiate two chains if the free radical reacted with hydrogen bromide to give an alkene and a bromine atom. Sherman, Quimby, and Sutherland (134)[15] have utilized such a chain-initiating step in calculating the activation energy of the addition of hydrogen bromide to vinyl bromide by the chain mechanism just described, and have arrived at a value of 29 kg-cal., one-half the estimated strength of the carbon–bromine bond. If this value is approximately correct, the abnormal addition can be initiated without the assistance of oxygen or peroxides. Such an activation energy, however, is probably higher than that for most normal addition reactions; hence appreciable abnormal addition of spontaneous origin could be expected only when the normal addition is very slow. Although oxygen and peroxides are usually responsible for the abnormal addition of hydrogen bromide to alkenes, it is futile at present either to assert or to deny that they are always entirely responsible. The significant aspects of the peroxide effect in additions of halogen acids are that abnormal addition takes place only with hydrogen bromide, and then by a chain mechanism, and that oxygen and peroxides are largely, if not entirely, responsible for this reaction.

6. *Other mechanisms proposed for abnormal addition*

The first mechanism to be proposed for abnormal addition was that of Urushibara and Takebayashi (155). Because iron and certain other metals also caused abnormal addition, they suggested that the effect of oxygen was due to its paramagnetic properties. The oxygen or metal was supposed to exert a physical influence on the surrounding alkene molecules such that the polarity of the double bond was affected. The shortcomings of this hypothesis have been mentioned elsewhere (87), and are admitted by at least one of the above workers (151), who now favors the bromine-atom chain mechanism.

Winstein and Lucas (165) have proposed an explanation for abnormal addition to a double bond the polarity of which (as indicated by the normal addition) is  $-\underset{+}{\overset{|}{C}}-\underset{-}{\overset{|}{C}}-$. They suggested that oxygen forms with

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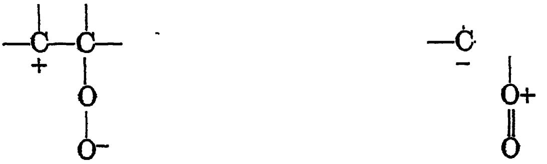
[15] These workers proposed the chain mechanism for both the normal and the abnormal additions of all halogen acids to alkenes a year before investigators in this laboratory suggested it only for the abnormal addition of hydrogen bromide.

double bonds of this type a complex represented by the following resonance forms:



If the second form makes the larger contribution to the complex, the proton of the attacking halogen acid attaches itself to the carbon atom which would have been relatively positive in the pure alkene. The oxygen is then displaced by a bromide ion, and abnormal addition results. Conn, Kistiakowsky, and Smith (20) concur essentially in this suggestion. However, such behavior of an oxygen molecule in forming successive loose complexes with several hundred molecules of alkene is not wholly consistent with the rapid irreversible reaction of oxygen on alkenes in the presence of hydrogen bromide (151).

Michael (114, 117) has recently attacked all previous mechanisms for abnormal addition and has suggested one of his own. On the basis that oxygen in the atmosphere or in the molecules of the solvents is negative, he proposes that oxygen from either source may become associated with the more positive of the doubly bound carbon atoms, thus making this atom relatively negative. If the effect of oxygen (or oxygen compound) is sufficient to reverse the polarity of the double bond, then the addition of halogen acid is also reversed.

All of these hypotheses may be said to account for an abnormal addition of hydrogen bromide, but all fail to indicate why hydrogen chloride and hydrogen iodide do not give a similar reaction. Further, all of them except that of Urushibara and Takebayashi fail to explain why some finely divided metals cause abnormal addition. This latter effect will soon be considered in the light of the chain mechanism.

7. *The influence of experimental conditions on additions of hydrogen bromide*

The following discussion of the effects of solvents, temperature, light, and metals on the liquid-phase addition of hydrogen bromide to alkenes will assume that all of the abnormal product results from addition of hydrogen bromide by the bromine-atom chain mechanism, whereas all of the normal product results from addition by other mechanisms. The reaction product obtained is the result of competition between the two mechanisms; hence its composition may vary from one extreme to the other. Experimental conditions may favor one mechanism and hinder the other, but the fact that the direction of addition of hydrogen chloride and hydrogen iodide has not yet been certainly (44, 84) altered by any agent indicates that these conditions affect the halogen acid or its mechanism of addition, and not the unsaturated compound.

Solvents principally affect the rate of the normal addition reaction. Because of the high order of this reaction, its rate is greatly decreased by dilution with inert solvents, and the abnormal addition may then outrun the normal reaction. This effect is strikingly demonstrated in the addition of hydrogen bromide to propene. When no solvent is used, the normal addition requires only a few minutes and abnormal addition is difficult to obtain, except in the presence of added peroxides (54). But when the reaction mixture is diluted with about ten volumes of pentane, abnormal addition is substantially complete[16] within half an hour at 0°C., even when the reaction mixture is prepared from purified materials in the absence of air (113). However, the addition of an antioxidant prevents abnormal addition; then several weeks are required for the normal reaction. Smith has shown that, at high dilution, the addition to undecenoic acid is highly sensitive to the presence of air (140). Both observations show clearly how dilution affects the competition between the two mechanisms, why past claims that a direct solvent effect is responsible for abnormal addition are open to serious doubt, and how a peroxide effect may be obtained with alkenes to which normal addition is rapid.

Small amounts of polar solvents such as water and acetic acid may increase the rate of the normal addition, probably because of dielectric effects and the change from a molecular to an ionic mechanism. This acceleration is partly responsible for the small amount of abnormal addition in polar solvents. Some solvents may, however, be weak inhibitors of abnormal addition, as will be indicated in the discussions of the temperature and light effects.

Table 8 summarizes work on the addition of hydrogen bromide to alkenes in solvents. All the experiments listed fulfill the following conditions: (*a*) they have been carried out since the discovery of the peroxide effect; (*b*) both products have been obtained in the same solvent by the same workers; (*c*) either addition product can be made to predominate by the suitable use of oxygen, peroxides, or antioxidants. The facts that a large variety of alkenes and solvents have been employed, and that many different workers have participated in obtaining these results, are convincing evidence that the mechanism of addition is the factor which determines the composition of the addition product.

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[16] Such a velocity would lead one to expect considerable abnormal addition in the absence of a solvent and of air, but no such reaction has actually been observed. If some association product of hydrogen bromide or propene or both is a weak inhibitor of abnormal addition, then this reaction, in agreement with qualitative indications, would be accelerated by dilution.

Some workers in the field disagree with the above conclusion, and maintain that solvents immediately affect the direction of addition, presumably through their effect on the polarity of the double bond. Gaubert, Linstead, and Rydon base their contention on the inability of diphenylamine to prevent formation of primary bromides from terminally unsaturated acids in hexane solution (25). Sherrill and coworkers (135, 136) insist that their 1-alkenes were peroxide-free and that the formation of primary bromides in solvents must therefore be a solvent effect. They used no antioxidants. Michael and coworkers claim to have demonstrated a solvent effect in the addition of hydrogen bromide to tetrolic and phenylpropiolic acids (table 3) and to trimethylethylene (table 8). In the first instance, they employed no antioxidants; in the second, the "solvent effect" was diminished by antioxidants and vanished in experiments with hydrogen chloride (table 1) or hydrogen iodide (table 2). The reviewers question not the experimental results of these workers, but their conclusions.

TABLE 8

Solvents in which hydrogen bromide yields either of two addition products

ALKENE	SOLVENTS EMPLOYED	REFERENCES
Allyl bromide	Water, 90% acetic acid, propionic acid, ligroin, carbon disulfide, chloroform, carbon tetrachloride, 1,2-dibromopropane, 1,3-dibromopropane, acetyl bromide*	(53)
Vinyl bromide	Acetic acid, nitrobenzene	(54)
Vinyl chloride	Acetic acid, nitrobenzene, mesitylene	(57)
Propene	Pentane, acetic acid	(60, 113)
1-Butene	Ligroin	(58)
1-Pentene	Pentane, propionic acid	(61)
Isobutylene	Pentane, carbon disulfide, propionic acid, ethyl bromide, benzonitrile, nitrobenzene, water	(65)
Trimethylethylene	Pentane, ethyl bromide, ether, methanol, ethanol, acetic acid*	(117, 162)
Styrene	Pentane	(162)
2-Bromo-2-butene	Acetic acid	(161)
2-Bromo-1-hexene	Benzene	(168)
Allylacetic acid	Hexane	(64)
Δ^{10}-Undecenoic acid	Ligroin, hexane, toluene, benzene, carbon disulfide, carbon tetrachloride, chloroform	(4, 35)
Ethyl Δ^{10}-undecenoate	Benzene, ligroin	(5)
Undecenyl acetate	Benzene, ligroin	(5)
Undecynoic acid	Benzene	(35)

* In the experiments indicated in these two solvents, less than 50 per cent abnormal addition in the presence of air or peroxides was observed.

An effect of the solvent on the polarity of the double bond, and thus on the direction of normal addition, would be most likely in instances where the normal addition product is a mixture, and where the directing effects of the substituents on the doubly bound carbon atoms are nearly balanced. No such effect has yet been reported with this type of ethylene derivative. The addition of hydrogen bromide to 2-pentene has been carried out without a solvent and in acetic acid solution (77). With Δ^9-undecenoic acid the reaction has been run in ligroin, hexane, benzene, and acetic acid (2, 34). In all cases, the addition product consisted, within experimental error, of equal proportions of the two possible halides. The fact that no solvent effect on the direction of normal addition has yet been established does not prove that none will ever be found, but the existence of such an effect should be demonstrated, not with hydrogen bromide (which is the only halogen acid capable of addition by an abnormal mechanism) but with hydrogen chloride or hydrogen iodide.

Increasing the reaction temperature generally increases the difficulty of eliminating abnormal addition. Air does not cause much abnormal addition to pure allyl bromide at 0°C., but it does at room temperature (53). Removal of air prevents abnormal addition at room temperature, but this procedure becomes ineffective at 76°C. However, the addition of an antioxidant reduces the proportion of abnormal addition product to about 10 per cent, even at 100°C., indicating that the effect of temperature is on the relative rates of the normal and abnormal addition reactions, and not on the allyl bromide (see footnote 3). Vinyl bromide (54) and vinyl chloride (57), to which the normal additions are slower, present similar difficulties beginning at lower temperatures, for antioxidants are always required to eliminate abnormal addition to these substances at room temperature, and partial failure of antioxidants has been observed at 46° and 76°C., respectively.

Abnormal addition to allyl bromide (53) and trimethylethylene (117) has been observed at -78°C. with small quantities of peroxides, showing that long chains are formed and that their propagation requires a negligible activation energy. Differences in the effectiveness of different antioxidants indicate that at least some, and probably all of them, require at least a small activation energy for reaction with bromine atoms. It follows that the proportion of effective collisions between a bromine atom and an antioxidant must increase as the temperature rises.[17] Therefore, the increasing predominance of abnormal addition at high temperatures in the presence of antioxidants cannot be ascribed to increased chain lengths, but must be due to the origin of many more chains. Although the

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[17] This phenomenon has been observed when alcohols, acetic acid, or acetyl bromide have been used as solvents; it will be described shortly.

decomposition of peroxides or their reaction with hydrogen bromide may have a high temperature coefficient, either reaction should lead to rapid exhaustion of traces of peroxides in experiments from which air has been excluded. Here the spontaneous origin of chains (i.e., without the influence of oxygen and peroxides), a reaction of high activation energy and high temperature coefficient, may become significant. The normal addition of hydrogen bromide to allyl bromide and vinyl bromide has a temperature coefficient of about 2 for 10°C. That of the abnormal addition is much larger, at least over certain ranges of temperature.

The temperature effect in solvents fits into the scheme already outlined. If the solvent (ligroin, chloroform, carbon tetrachloride with allyl bromide (53), ether with trimethylethylene (117)) decreases the rate of normal reaction, then the abnormal addition becomes more prominent and appears at a lower temperature. If the solvent (acetic acid, water, acetyl bromide with allyl bromide) increases the rate of the normal reaction, then abnormal addition becomes less prominent.

The fact that abnormal addition is easily obtained in many solvents indicates that their inhibiting properties are usually negligible. Nevertheless, almost any of the aliphatic solvents in table 8 can react with bromine atoms, as shown by the mechanism of aliphatic substitution. In the solvents which inhibit, the effect increases with increasing temperature. In the presence of peroxides, no abnormal addition to trimethylethylene takes place in ethanol solution at 20°C. or in methanol at 0°C., but the proportion of abnormal addition increases at lower temperatures (117). Acetic acid and acetyl bromide seem to have definite inhibiting properties in additions to allyl bromide at 76°C.; moreover, in the light, acetic acid seems to be a better inhibitor of abnormal addition at 25°C. than at 10°C. Ordinarily, little difficulty is encountered in obtaining abnormal addition in glacial acetic acid (*cf.* table 8), but experiments with allyl bromide in this solvent show that small amounts of admixed water favor abnormal addition.

Light accelerates both the normal and the abnormal additions of hydrogen bromide to allyl bromide (53) and vinyl bromide (54), but the effect on the abnormal addition is usually far greater than on the normal reaction. The rate of addition to allyl bromide in the light is greatest in the presence of air, slower in the absence of air, and still slower in the presence of added antioxidants. In the first two instances, the abnormal addition product is formed exclusively; in the last, predominantly. These observations are corroborated by others made on vinyl chloride (57) and trichloroethylene (74).

In additions to allyl bromide in the light, the effects of various spectral regions and of solvents have been investigated. In the absence of air and antioxidants, abnormal addition was substantially complete in 1 to 4 hr., regardless of whether the light supplied was near ultraviolet, red and infrared together, or a combination of either with visible light.[18] In the presence of 1.4 mole per cent of diphenylamine, a combination of red and infrared light was clearly shown to accelerate the normal addition by a factor of 5 to 10 without causing much abnormal addition. Visible and near ultraviolet radiation gave increasing proportions (up to 74 per cent) of abnormal addition product at about the same total reaction rate. Thus the shorter wave lengths make repression of abnormal addition more difficult. In the absence of air and antioxidants, abnormal addition occurs exclusively when heptane, carbon disulfide, acetyl bromide, or benzoyl chloride are used as solvents. In acetic acid solution, only very small proportions of abnormal addition product are obtained; none of this product is formed in the presence of hydroquinone. Comparison of these experiments with those carried out in the absence of a solvent indicates that acetic acid has some inhibiting properties for the abnormal addition, and that the effect of light on the competition between the normal and abnormal reactions is much like that of increased temperature.

Inasmuch as the individual effects of light and temperature on the rates of the normal and abnormal additions are known only qualitatively, and since the effects of temperature on the inhibiting properties of solvents and antioxidants have not been isolated, the combined effects of light and temperature cannot yet be completely resolved. The effect of lowering the reaction temperature in the photochemical addition of hydrogen bromide to vinyl bromide (54) is impressive. Although no normal addition occurs at room temperature in the presence of antioxidants, a 50 to 60 per cent yield of an 80 per cent normal product was obtained in 16 hr. at 5°C. Thus not only was the proportion of abnormal addition greatly reduced by lowering the temperature, but the normal addition product was formed at the rate of about 3 per cent per hour, as against 1 per cent per day in the dark at room temperature,—an increase by a factor of about 70 in spite of a 20°C. temperature decrease. The case of allyl bromide is less clear-cut. The effect of light in accelerating the normal addition is smaller, and lowering the reaction temperature in the presence of antioxidants does not significantly increase the proportion of normal addition product.[19] The available data do not permit estimation of the

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[18] Comparisons of rates are not possible, because the amount of light transmitted by the filters is not known.

[19] Kharasch and Mayo (53), using thiocresol as an antioxidant, observed 71 per cent and 30 per cent normal addition at 5°C. and at room temperature, respectively, but in view of the fact that the combined yields of both addition products were 54 per cent and 91 per cent, respectively, and that normal addition is fastest during

effect of light on the rates of the two possible additions in glacial acetic acid solution, but they show conclusively that in the light more abnormal addition takes place at 5°C. than at room temperature. This fact can be explained by the assumption that acetic acid is less effective as an inhibitor at lower temperatures. Such a conclusion is consistent with observations made at higher temperatures or in the presence of alcohols. It may be noted that at 5°C. a reaction mixture containing diphenylamine reacted more slowly than one containing oxygen and gave slightly less abnormal addition product,—a fact which may be taken to indicate that the effect of light in accelerating the abnormal addition is large compared with that of oxygen.

The acceleration of both the normal and abnormal addition by light, the increased light effect in the presence of oxygen, some relations between the combined effects of light and temperature, and the partial and variable effects of antioxidants in repressing abnormal addition in the light all show the close analogy between the effect of light and that of increased temperature. These observations are consistent with the concept that all abnormal addition products result from a reaction by the chain mechanism. Since the effect of light is greatest in the presence of oxygen, illumination apparently accelerates peroxide formation and oxidation of hydrogen bromide, but it apparently also serves to initiate chains without the assistance of oxygen. The fact that light accelerates the normal (as well as the abnormal) addition, and that the effect is much greater with vinyl bromide than with allyl bromide, shows that either the alkene, its complex with hydrogen bromide, or some impurity absorbs visible radiation. The greater effectiveness of the shorter wave lengths in accelerating abnormal addition to allyl bromide is consistent with the greater activation energy of this reaction. Although in the absence of air and peroxides, reaction mixtures usually remain colorless in the dark, the presence of oxygen, peroxides, or light usually leads to the development of variable quantities of dark-colored materials. These may assist in the transference of energy to substances which otherwise absorb only weakly.

It was found by Urushibara and Takebayashi that, if the addition of hydrogen bromide to allyl bromide takes place in the presence of finely divided and freshly reduced iron, nickel, or cobalt, varying quantities of abnormal product are formed, even in the presence of some antioxidants.

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the first part of the reaction when the concentrations of reactants are highest, the conclusion that temperature lowering increases the yield of normal addition product is not justified. A recent experiment with catechol at 5–10°C. (112) gave in 65 hr. a 92 per cent yield of a mixture containing only 26 per cent of the normal addition product, again indicating that temperature lowering may have no marked effect.

They observed similar phenomena when hydrogen bromide was added to undecenoic acid in toluene solution. Their work has been reviewed elsewhere (151) and that portion of it concerned with the effect of reduced iron on allyl bromide has been confirmed, extended, and explained in a paper from this laboratory (87). The complete inhibition of the iron-promoted abnormal addition by some antioxidants, and its partial inhibition by others (*cf.* table 6), are strong indications that abnormal addition is the result of the bromine-atom chain mechanism. The fact that some hydrogen and metal bromide are formed suggests that interaction of the metal with hydrogen bromide or allyl bromide yields some hydrogen atoms or free radicals. Reaction of hydrogen atoms with hydrogen bromide or allyl bromide would yield free radicals or bromine atoms, either of which might initiate chains for the abnormal addition.

$$\mathrm{Fe + HBr \rightarrow FeBr\cdot + H\cdot} \tag{8}$$

$$\mathrm{RCH{=}CH_2 + H\cdot \rightarrow R\underset{\bullet}{C}HCH_3} \tag{9}$$

$$\mathrm{H\cdot + HBr \rightarrow H_2 + Br\cdot} \tag{10}$$

$$\mathrm{Fe + R'Br \rightarrow FeBr^{\bullet} + R'\cdot} \tag{11}$$

Thus far, iron-promoted abnormal addition has not been found with any alkene which gives a rapid normal addition with hydrogen bromide, but it has been observed with allyl chloride and possibly with vinyl bromide. Other metals have failed to cause abnormal addition to allyl bromide, because they do not react with anhydrous hydrogen bromide, because the bromides formed are strong catalysts for the normal addition (section I, A, 3), or because their bromides are strong inhibitors for the abnormal reaction (table 6).

The success of the bromine-atom chain mechanism in correlating the metal effect with the peroxide effect, an advantage not possessed by any other mechanism yet proposed for either reaction, is a strong point in favor of this interpretation. However, the value of a hypothesis lies in its ability to predict new reactions as well as to explain known ones. At the end of this paper, it will be shown how many new applications of this concept have been developed since it was first formulated.

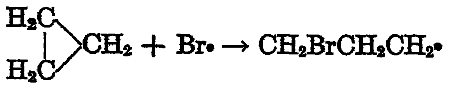
In concluding this section dealing with the influence of experimental conditions on the direction of addition, the conditions which should be chosen to promote either normal or abnormal addition of hydrogen bromide are summarized. To favor normal addition, this reaction may be accelerated by the use of high concentrations of reactants, particularly hydrogen bromide, or by the use of fairly small proportions of polar solvents (acetic acid), or of catalysts (ferric and aluminum bromides); and the abnormal addition can be inhibited by the use of antioxidants. To favor abnormal addition, this reaction may be accelerated by the use of oxygen, peroxides, certain metals (iron, nickel), light, or elevated temperatures; the normal addition (unless it is naturally slow) should be retarded by dilution with inert, non-polar solvents. It should be added that any atom or free radical which can react with the hydrogen atom or the bromine atom of hydrogen bromide or with an alkene may be capable of starting a reaction chain.

8. The addition of hydrogen bromide to cyclopropane

Cyclopropane is closely related to propene, in that both react with some acids and oxidizing agents to give propane derivatives. They differ in that cyclopropane gives 1,3-derivatives of propane, whereas propene gives 1,2-derivatives. In an investigation of the addition of hydrogen bromide to cyclopropane (78), although the product was always *n*-propyl bromide, striking analogies with addition to alkenes were found in rates of reaction.

When equimolecular mixtures of cyclopropane and hydrogen bromide were allowed to react in sealed tubes at room temperature in the absence of air and light, 50 to 60 per cent reaction took place in 4 hr. If 3 mole per cent of water or acetic acid was added to the mixture, about 90 per cent reaction took place in the same period, indicating that addition occurred largely through a polar molecular or ionic mechanism like that for the normal addition of halogen acids to alkenes. Similar proportions of catechol or thiocresol acted like water or acetic acid, but oxygen or visible light had only a small accelerating effect on the reaction. However, if the reaction mixture was made up of 10 moles of cyclopropane to 1 mole of hydrogen bromide, thus in effect diluting the previous reaction mixtures with 9 moles of hydrocarbon, then characteristics of the abnormal addition of hydrogen bromide to alkenes appeared. In the absence of oxygen and light, only 8 per cent reaction took place in 2 hr. Light alone increased this yield to 11 to 12 per cent; oxygen alone, to 81 per cent; oxygen and light together, to 99 per cent; peroxides and light, to 74 per cent. Catechol and diphenylamine had small to moderate inhibiting effects on the accelerated reaction. That the effects were not larger is due to the fact that the antioxidants (and also water) accelerated addition by favoring the competing normal mechanism, as in concentrated solution.

These phenomena suggest that oxygen and peroxides react with hydrogen bromide to give bromine atoms, or with cyclopropane to give free radicals, and that addition of hydrogen bromide may then take place through the following chain mechanism:



$$\begin{matrix}H_2C\\ |\\ H_2C\end{matrix}\!>\!CH_2 + Br\cdot \rightarrow CH_2BrCH_2CH_2\cdot \qquad (12)$$

$$CH_2BrCH_2CH_2\cdot + HBr \rightarrow CH_2BrCH_2CH_3 + Br\cdot \qquad (13)$$

In additions of hydrogen bromide to pure alkenes, light is more powerful than oxygen in promoting abnormal addition, but the reverse is true for cyclopropane. Hence the analogy between alkenes and this compound is not complete. Possibly the chain may require modification to include oxygen (78).

III. THE ADDITION OF MERCAPTANS AND THIO ACIDS TO UNSATURATED COMPOUNDS

A. INTRODUCTION

A mercaptan, like a halogen acid, when it is added to an unsymmetrically substituted ethylene bond, can yield either of two products:

$$RCH{=}CH_2 + R'SH \rightarrow RCH_2CH_2SR' \text{ (abnormal addition)} \qquad (14)$$

$$RCH{=}CH_2 + R'SH \rightarrow RCH(CH_3)SR' \text{ (normal addition)} \qquad (15)$$

These two possible reactions are here designated "normal" and "abnormal" additions on the assumption that mercaptans should add like halogen acids. Actually, both additions have been recorded, but when the absorbing compound is a hydrocarbon, the abnormal addition reaction is the one commonly observed when no catalysts for the normal addition are employed. This fact accounts for the acceptance of the rule prematurely proposed by Posner (125) for the addition of mercaptans to alkenes: namely, that the sulfur becomes attached to the carbon atom holding the most hydrogen atoms. The products and mechanism of the abnormal addition of mercaptans to alkenes will be first discussed; then those of the normal addition reaction. It will be shown that both have much in common with the additions of hydrogen bromide. Finally, the range of applicability of both reactions will be indicated.

Although mercaptans usually add abnormally, there is no evidence of such an addition for hydrogen sulfide, which adds only at fairly high temperatures. Under pressure and below 200°C., all the mercaptans and sulfides obtained are normal addition products, and their formation is catalyzed by sulfur (45, 49). The vapor-phase reaction at atmospheric pressure has been studied at 200–300°C. over a nickel–kieselguhr catalyst (9) and at 300°C. over silica gel (108). In the first instance, 5 to 25 per cent of a mixture containing about 65 per cent of isopropyl mercaptan and 35 per cent of *n*-propyl mercaptan was obtained from propene. This reaction product was considered to be an equilibrium mixture of the two possible addition products (*cf.* footnote 3). In the second instance, mercaptans, sulfides, and thiophene derivatives of unknown structure were obtained.

B. THE ABNORMAL ADDITION OF MERCAPTANS AND THIO ACIDS

It has been clearly shown (6, 16, 49, 76) that the abnormal addition of mercaptans to alkenes is catalyzed by oxygen and peroxides, that it is inhibited by hydroquinone and piperidine, and that it is accelerated by light. The peroxides formed when an alkene is exposed to air are sufficient to catalyze the abnormal addition; careful purification of the reactants and exclusion of air prevents, or greatly retards, any addition. Table 9 summarizes the evidence that the abnormal addition of mercaptans to alkenes can be inhibited by antioxidants, and initiated by oxygen or peroxides, particularly in the presence of light. It is therefore a chain reaction. The structures of the products formed also supply excellent evidence that the addition does not proceed through a polar or ionic mechanism. Table 10 lists other reactions which show that abnormal addition products are commonly formed when air is not excluded. Table 9 records two instances in which both normal and abnormal addition products are formed, although the latter predominate. In every other addition listed in either table, the abnormal addition product is formed exclusively. The known examples include both aliphatic and aromatic mercaptans, mercaptoacetic acid, and thioacetic acid; the alkenes contain aromatic and aliphatic substituents, but all except trimethylethylene have terminal double bonds.

In 1934, Burkhardt (16) mentioned that the abnormal addition of thiophenol to styrene might be due to the presence of "sulfur in a positive ion or in an oxidizing form," possibly as a free radical, and possibly through a chain reaction. A more definite proposal that the abnormal addition takes place through a chain reaction involving free radicals was subsequently made from this laboratory (76):

$$\mathrm{RSH} + \mathrm{O_2}\ \text{(or peroxide)} \xrightarrow{\text{(alkene)}} \mathrm{RS}\cdot + \mathrm{HO_2}\cdot \qquad (16)$$

$$\mathrm{RS}\cdot + \mathrm{R'CH{=}CH_2} \rightarrow \mathrm{R'}\underset{\bullet}{\mathrm{C}}\mathrm{HCH_2SR} \quad (\Delta H = 13\ \text{kg-cal. per mole}) \qquad (17)$$

$$\mathrm{R'}\underset{\bullet}{\mathrm{C}}\mathrm{HCH_2SR} + \mathrm{RSH} \rightarrow \mathrm{R'CH_2CH_2SR} + \mathrm{RS}\cdot \ (\Delta H = 0) \qquad (18)$$

The effects of oxygen, peroxides, light, and antioxidants and the nature of the addition product so resemble those observed in the abnormal addition of hydrogen bromide that little further comment on these points is necessary. In both instances, the heats of reaction of the corresponding steps, as calculated from estimated bond energies (124), are almost identical (*cf.* table 7). The well-known easy oxidation of mercaptans to disulfides and the suggested dissociation of disulfides into free radicals (132) further support the mechanism suggested.

Substantial addition of mercaptoacetic acid to styrene in the absence

TABLE

Evidence of abnormal addition of mercaptans to alkenes

ALKENE	MERCAPTAN	EXPERIMENTAL CONDITIONS*	ADDITION PRODUCT	EVIDENCE OF MECHANISM	REFERENCES
$C_6H_5CH{=}CH_2$	C_6H_5SH	a	$C_6H_5CH_2CH_2SC_6H_5$ (<2% isomer)	Accelerated by light and air; inhibited by piperidine	(6)
$C_6H_5CH{=}CH_2$	CH_3SH	a	$C_6H_5CH_2CH_2SCH_3$	Accelerated by light and oxygen	(51)
$CH_3CH{=}CH_2$	C_2H_5SH	b	*n*-$C_3H_7SC_2H_5$ (50%) *i*-$C_3H_7SC_2H_5$ (14%)	Ascaridole as catalyst†	(49)
1-Octene	C_2H_5SH	b	*n*-$C_8H_{17}SC_2H_5$ (28%) $C_6H_{13}\underset{\displaystyle CH_3}{\underset{\vert}{C}}HSC_2H_5$ (4%)	Alkene peroxide or ascaridole as catalyst†; only 4 to 5% total sulfides in presence of hydroquinone	(49)
$RCH{=}CH_2$ (R equals $CH_3(CH_2)_n$, where $n = 8$, 10, 12, 14, 16)	R′SH (R′ equals *n*-$C_{12}H_{25}$–, phenyl, *p*-tolyl, or β-naphthyl	b	RCH_2CH_2SR' (nearly quantitatively)	Alkene peroxide as catalyst. Lauryl mercaptan gave < 10% sulfides in presence of hydroquinone.† Thiocresol and peroxide-free tridecene alone gave very small yield; with ascaridole, a good yield	(49)
$CH_3(CH_2)_{10}CH{=}CH_2$	$HS(CH_2)_nSH$ ($n = 2$ to 12, 18)	b	$CH_3(CH_2)_{12}S(CH_2)_nS(CH_2)_{12}CH_3$ (nearly quantitatively except when $n = 18$)	Alkene peroxide as catalyst	(49)
n-$C_{12}H_{25}SCH_2CH{=}CH_2$	*n*-$C_{12}H_{25}SH$	b	*n*-$C_{12}H_{25}S(CH_2)_3SC_{12}H_{25}(n)$	Ascaridole as catalyst	(49)
$C_6H_5CH{=}CH_2$	$HSCH_2COOH$	a	$C_6H_5CH_2CH_2SCH_2COOH$	Rapid reaction in presence of ascaridole as catalyst. No reaction in absence of air and presence of hydroquinone	(76)
$(CH_3)_2C{=}CH_2$	$HSCH_2COOH$	a	*i*-$C_4H_9SCH_2COOH$		(76)
$CH_2OHCH{=}CH_2$	CH_3SH	a	$HO(CH_2)_3SCH_3$	Accelerated by oxygen and light; inhibited by piperidine, sulfuric acid; mercury salts had various effects	(50)

* a = reaction in absence of solvent at or near room temperature; b = reaction for 10 hr. in sealed vessel at 180°C. in absence of a solvent.

† Different product obtained without this catalyst; *cf.* table 11.

TABLE 10

Abnormal additions of mercaptans and thio acids to alkenes

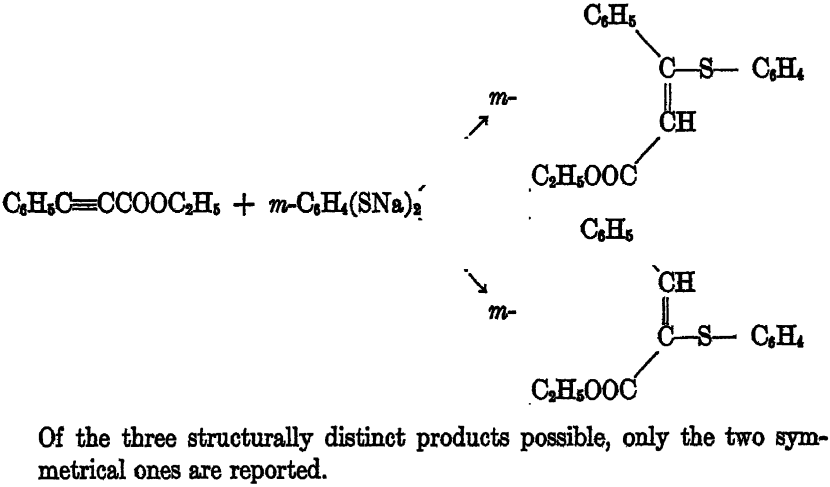
ALKENE	MERCAPTAN OR THIO ACID	TEMPERATURE	ADDITION PRODUCT	REFERENCES
		°C.		
$CH_3CH{=}CH_2$	C_6H_5SH	120	n-$C_3H_7SC_6H_5$ (60%)	(47)
$C_2H_5CH{=}CH_2$	C_6H_5SH	100	n-$C_4H_9SC_6H_5$ (73%)	(47)
$(CH_3)_2C{=}CH_2$	C_6H_5SH	20	i-$C_4H_9SC_6H_5$ (90%)	(47)
n-$C_3H_7CH{=}CH_2$	C_6H_5SH	50	n-$C_5H_{11}SC_6H_5$ (25%)	(47)
i-$C_3H_7CH{=}CH_2$	C_6H_5SH	55	i-$C_3H_7CH_2CH_2SC_6H_5$ (80%)	(47)
$(CH_3)_2C{=}CHCH_3$	C_6H_5SH	Room temperature	$(CH_3)_2CHCH(CH_3)SC_6H_5$* (60%)	(47)
$CH_3CH{=}CH_2$	C_2H_5SH	100	n-$C_3H_7SC_2H_5$ (64%)	(45)
$(CH_3)_2C{=}CH_2$	C_2H_5SH	100	i-$C_4H_9SC_2H_5$ (94%)	(45)
i-$C_3H_7CH{=}CH_2$	C_2H_5SH	Room temperature	i-$C_3H_7CH_2CH_2SC_2H_5$ (5%)	(45)
$(CH_3)_2C{=}CHCH_3$	C_2H_5SH	Room temperature	i-$C_3H_7CH(CH_3)SC_2H_5$ (90%)	(45)
$(CH_3)_2C{=}CH_2$	n-C_4H_9SH	100	i-$C_4H_9SC_4H_9$(n) (66%)	(45)
$(CH_3)_2C{=}CH_2$	CH_3COSH	100	i-$C_4H_9SCOCH_3$ (60%)	(45)
i-$C_3H_7CH{=}CH_2$	CH_3COSH	100	i-$C_3H_7CH_2CH_2SCOCH_3$ (86%)	(45)
$(CH_3)_2C{=}CHCH_3$	CH_3COSH	70	i-$C_3H_7CH(CH_3)SCOCH_3$ (87%)	(45)
$C_6H_5CH{=}CH_2$	CH_3COSH	Room temperature	$C_6H_5CH_2CH_2SCOCH_3$ (85%)	(41)

* Different addition product obtained under other conditions; *cf.* table 11.

of solvents requires a few minutes (76) or a few hours (40) at room temperature, the rate apparently depending upon the purity of the materials and the presence of light. The addition is said to be about as fast in glacial acetic acid solution as in the absence of a solvent, but it is much slower in benzene (40). There is accordingly a difference between hydrogen bromide and mercaptans with respect to the effect exerted by inert solvents on the rates of the respective abnormal additions of these substances.

C. THE NORMAL ADDITION OF MERCAPTANS

Until recently, the only examples of normal addition of mercaptans to double bonds involved alkenes in which these bonds were conjugated with carbonyl groups, and there only the normal addition was observed. The hydrogen of the mercaptan becomes attached to the α-carbon atom and the sulfur to the β-carbon atom of the unsaturated acid or ketone (121, 145). Such additions are catalyzed by both acids (hydrogen chloride in acetic acid) and bases (piperidine or sodium ethylate). The unilateral addition of mercaptans to such double bonds agrees closely with the behavior of hydrogen bromide; so also does the formation of two products in the one known instance of addition to a triple bond conjugated with a carbonyl group. The following reaction is reported to occur in toluene solution at room temperature (22):



(19)

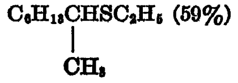
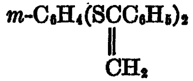
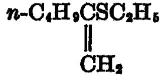
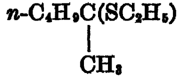
(20)

Of the three structurally distinct products possible, only the two symmetrical ones are reported.

Table 11 summarizes normal additions of mercaptans to hydrocarbons, a catalyst being required in every case. Jones and Reid (49) found that sulfur catalyzes the normal addition; Ipatieff, Pines, and Friedman state that sulfuric acid is also effective. The use of sulfuric acid was introduced by Posner (125), who, however, thought that it accelerated the abnormal addition. The mechanism of normal addition of mercaptans is unknown,

TABLE 11

Normal additions of mercaptans to alkenes and alkynes

ALKENE OR ALKYNE	MERCAPTAN	EXPERIMENTAL CONDITIONS*	ADDITION PRODUCT	EVIDENCE OF MECHANISM	REFERENCES
$CH_3CH{=}CH_2$	C_2H_5SH	b	$i\text{-}C_3H_7SC_2H_5$ (82%) $n\text{-}C_3H_7SC_2H_5$ (8%)	Sulfur as catalyst†; no reaction in absence of sulfur	(49)
1-Octene	C_2H_5SH	b	 $C_6H_{13}\underset{\underset{CH_3}{\mid}}{C}HSC_2H_5$ (59%)	Sulfur as catalyst†	(49)
$CH_3CH{=}CH_2$	C_6H_5SH	b	$i\text{-}C_3H_7SC_6H_5$ (*ca.* 35%)	Sulfur as catalyst	(49)
$RCH{=}CH_2$	$C_{12}H_{25}SH$	b	Mixture	Sulfur as catalyst†	(49)
$(CH_3)_2C{=}CH_2$	$t\text{-}C_4H_9SH$	c	$(t\text{-}C_4H_9)_2S$	Nickel, cobalt, or iron sulfide as catalyst	(3)
$(CH_3)_2C{=}CH_2$	C_6H_5SH	a	$t\text{-}C_4H_9SC_6H_5$ (70%)	75% sulfuric acid as solvent and catalyst†	(47)
$(CH_3)_2C{=}CHCH_3$	C_6H_5SH	a	$t\text{-}C_5H_{11}SC_6H_5$ (60%)	20% sulfuric acid in acetic acid as solvent and catalyst†	(47)
$C_6H_5C{\equiv}CH$	$m\text{-}C_6H_4(SH)_2$	a	 $m\text{-}C_6H_4(S\underset{\underset{CH_2}{\Vert}}{C}C_6H_5)_2$	Sodium salt of mercaptan used	(22)
$n\text{-}C_4H_9C{\equiv}CH$	C_2H_5SH	b	 $n\text{-}C_4H_9\underset{\underset{CH_2}{\Vert}}{C}SC_2H_5$ and  $n\text{-}C_4H_9\underset{\underset{CH_3}{\mid}}{C}(SC_2H_5)_2$	Sulfur as catalyst; structures not proved	(49)

* a = reaction at room temperature; b = reaction for 10 hr. in sealed vessel at 180°C. in absence of solvent; c = reaction under pressure at 35–200°C. (patent claim).

† Different product obtained without this catalyst; *cf.* table 9 or 10.

but several analogies to the normal additions of halogen acids can be pointed out: (*a*) The catalysis of mercaptan addition by sulfuric acid resembles the participation of two molecules of halogen acid in the addition of one such molecule, and suggests that the alkene–acid complex reacts with mercaptan. (*b*) The catalysis of mercaptan addition by bases recalls the accelerating effect of ammonium salts on halogen acid additions, and suggests that mercaptide ion may sometimes participate in the reaction. (*c*) Catalysis by sulfur resembles the catalysis of hydrogen iodide addition by iodine. (*d*) Catalysis by metal sulfides is somewhat analogous to catalysis of halogen acid additions by metal halides.

The fact that an alkene is symmetrically substituted does not prevent the addition of a mercaptan from taking place through two distinct mechanisms. The addition of ethyl mercaptan to cyclohexene is catalyzed by either peroxides or sulfur, although cyclohexyl ethyl sulfide is the only possible product. Peroxide catalysis is prevented by hydroquinone, with the result that no addition takes place (49).

D. SCOPE OF THE MERCAPTAN–ALKENE REACTION

The following work is cited to indicate the applicability of the mercaptan–alkene reaction, but, except in additions to ethylene, the structures of the addition products have not been established. Posner (125) found that thiophenol or benzyl mercaptan would add to a large number of solid and liquid hydrocarbons, the only exceptions noted being stilbene and 1,4-diphenylbutadiene. He obtained no significant addition to ethylene or propene at ordinary temperatures, but Jones and Reid (49) added ethyl mercaptan and trimethylene dimercaptan to ethylene at high temperatures and pressures in the presence of sulfur. Von Braun and Plate (13) explained the ready polymerization of allyl, crotyl, furfuryl, and cinnamyl mercaptans by the interaction of sulfhydryl groups with double bonds. Holmberg (40) found that mercaptoacetic acid added readily to cinnamyl alcohol, its acetate, and its benzoate. The ready addition of mercaptoacetic acid to many unsaturated compounds and the easy estimation of the sulfhydryl group have led to the use of this reaction in the determination of the degree of unsaturation in oils, fats (7), and gasoline (42). It is stated that peroxides in the latter instance retard the reaction of 2-octene, a claim not in accord with any other available information.

Morgan and Friedman (118) have studied the rate and extent of addition of mercaptoacetic acid, cysteine, and glutathione to maleic acid. They used evacuated reaction tubes and buffered aqueous solutions of sodium salts at a pH of 7.4 and a temperature of 37°C. Part of the maleic acid which did not react was isomerized to fumaric acid, a point to be considered in a later section. However, none of these mercaptan derivatives was found to add to fumaric, citraconic, mesaconic, or α-phenyl-β-styrylmaleic acids or to *cis*- and *trans*-cinnamic acids.

IV. THE REACTION OF BISULFITES WITH UNSATURATED COMPOUNDS

A. INTRODUCTION

It has long been known that ammonium and alkali-metal bisulfites in aqueous solution add to carbon double bonds, thus forming alkyl sulfonates:

$$R_1R_2C{=}CR_3R_4 + NaHSO_3 \rightarrow R_1R_2CHCR_3R_4(SO_3Na) \qquad (21)$$

Until recently, the best-known of these additions were those to aldehydes, ketones, and acids unsaturated in the α,β-positions (144). Here the products were exclusively those which correspond to the ones obtained by normal addition of halogen acids,—the proton going to the α-carbon atom, the sulfonate group to the β-carbon atom. It has also been shown that bisulfites sometimes add to double bonds in alcohols, in aldehydes, and in liquid and gaseous hydrocarbons where these bonds are not conjugated with carbonyl groups (for references see 75, 144), but the structures of most of the products are unknown. Ethylene and cyclohexene give only one addition product; allyl alcohol was concluded to yield 3-hydroxypropyl-1-sulfonate; the structure assigned to the styrene addition product (6) was in error (75).

Kolker and Lapworth (100) shook their reaction mixtures with kieselguhr in order to maintain contact between hydrocarbon and water solution, and thus obtained addition products from several hydrocarbons. They noted that dilution of the bisulfite solution favored reaction. Other workers found that refluxing the reactants was sometimes successful; still others reported that reaction often failed to take place in sealed tubes, even at higher temperatures. Some of these observations suggested that the addition of bisulfite to unconjugated double bonds may take place through a radical-chain mechanism, and subsequent work agrees with this hypothesis. Since the reaction with aliphatic double bonds seems to consist mostly, if not entirely, of simple addition, it will be discussed first. The more complicated reaction with styrene will be considered later.

B. THE ADDITION OF BISULFITES TO ALIPHATIC UNSATURATED COMPOUNDS

The work dealing with the effect of oxidizing agents on the addition of bisulfites to alkenes has been carried out largely in this laboratory; the three different techniques employed will be indicated. Except with allyl alcohol, all the additions of bisulfites were carried out at room temperature.

Bisulfites were added to ethylene, propene, and isobutylene (75, 29) by shaking an aqueous solution of the salts with the gas under pressures of 15 to 40 pounds per square inch. Under these conditions the gases in question did not react with bisulfites in the absence of oxygen. Admission of a little air permitted reaction to proceed only temporarily, and repeated intermittent admissions were required to obtain substantially complete reaction of the bisulfite. Based on the amount of bisulfite consumed, propene and isobutylene gave as much as 55 per cent and 62 per cent, respectively, of organic sulfonates, the remainder of the salt being oxidized to bisulfate. Ethylene gave lower yields. The products isolated were exclusively the primary sulfonates, corresponding to an abnormal addition of hydrogen bromide or mercaptan. No normal addition of bisulfite is known where the double bond is not conjugated with a carbonyl group. When such conjugation occurs, there is no peroxide effect; experiments with crotonic acid (96) show that, just as in hydrogen bromide additions, oxygen here has no effect either on the rate or the direction of addition.

Liquid cyclohexene, 2-pentene, trimethylethylene, 2,4,4-trimethyl-2-pentene, isoprene, and pinene were shaken with bisulfite solutions under constant oxygen pressures (130). Oxygen was consumed slowly during the course of the reaction, and, if the supply was interrupted, interaction of the hydrocarbon with bisulfite also stopped. The first three of the substances named gave as much as 90 per cent or more of sulfonates, the yields being greatest at 30 mm. of oxygen and decreasing progressively at 152 or 760 mm. The last three alkenes reacted less easily and gave yields of only 15 to 20 per cent. Cyclohexene gave a cyclohexylsulfonate; no other addition products were identified. The product from isoprene still contained one double bond; that from pinene was unstable. Trimethylethylene and 2-pentene seemed to give mixtures of sulfonates.

Additions to allyl alcohol were carried out in sealed tubes at 100°C. (75). Evacuation of these tubes did not prevent addition, but when 10 mole per cent of hydroquinone was added to the reaction mixture before evacuation, no reaction occurred. In the presence of oxygen, up to 65 per cent of sodium 3-hydroxypropane-1-sulfonate was obtained, as demonstrated by conversion of the product to 3-chloropropane-1-sulfonamide. On the assumption that unsymmetrical reagents add to allyl alcohol in the same way that they add to the allyl halides, the above addition to allyl alcohol is abnormal.

In additions to both propene (75) and the liquid alkenes (130), sodium or ammonium nitrites, which are also capable of oxidizing bisulfites, have been found to exert an effect like that of oxygen. In experiments with cychlohexene, 0.06 mole of nitrite per mole of bisulfite, introduced slowly over a long period, gave 84 per cent sulfonate, whereas a larger proportion of nitrite (0.1 mole), introduced all at once, gave only 55 per cent yield. In an experiment with trimethylethylene, 0.005 mole of sodium nitrite per mole of bisulfite gave 90 per cent yield of addition product, indicating that about 180 molecules of organic sulfonate were formed per molecule of nitrite reduced.

It has already been shown by Franck and Haber (23) and by Bäckström (8) that the oxidation of sulfite and bisulfite are chain reactions involving the $\bullet SO_3^-$ ion radical and the $\bullet HSO_3$ radical. The necessity for using oxygen or other oxidizing agents in the addition reaction, the small proportion of agent required, and the advantage of introducing this agent gradually, as well as the inhibition of the reaction by hydroquinone, and the fact that the product corresponds to an abnormal addition, all suggest a chain reaction involving free radicals (75):

$$SO_3^{--} + \text{oxidant} \rightarrow \bullet SO_3^- + \text{oxidant}^- \tag{22}$$

$$\bullet SO_3^- + RCH{=}CH_2 \rightarrow R\underset{\bullet}{C}HCH_2SO_3^- \tag{23}$$

$$R\underset{\bullet}{C}HCH_2SO_3^- + HSO_3^- \rightarrow RCH_2CH_2SO_3^- + \bullet SO_3^- \tag{24}$$

The extent to which the sulfite-ion radical and the sulfonate-ion radical may be associated with a proton is not known. The range of pH over which addition can take place suggests that either or both charged and uncharged radicals may participate.

The oxidation of bisulfite to bisulfate during oxygen-catalyzed additions causes an increase in the acidity of the solution and a retardation of the addition. The increase in acidity can be overcome by substituting sulfite for that part of the bisulfite oxidized, so that normal sulfate rather than bisulfate is formed. If too large a proportion of sulfite is used, some of this substance adds to the alkene, thus liberating an equivalent of alkali which also retards the addition reaction. If the ratio of sulfite to bisulfite in the initial solution is the same as the ratio of sulfate to sulfonate in the reaction products, then the pH of the sulfite–bisulfite buffer remains practically constant and the addition of bisulfite proceeds at a maximum rate and to a maximum extent. This optimum proportion of sulfite to bisulfite varies with both the rate of oxidation and of addition, and therefore depends upon the concentration of sulfite, the alkene used, and the other experimental conditions. The pH of the sulfite–bisulfite buffer depends upon the sulfite–bisulfite ratio and on the cation.

Although the pH of such buffers is thus of little theoretical significance, some representative data are cited here. In the addition to cyclohexene, using oxygen at 1 atm. pressure, the optimum pH of a sodium salt buffer was about 6.4 and that of a similar ammonium salt buffer about 6.0 (130). In additions to propene, oxygen was supplied intermittently; the optimum pH of a sodium salt buffer was 5.8 (76.5 per cent bisulfite, 23.5 per cent sulfite), and that of an ammonium salt buffer was 6.0 (55 per cent bisulfite, 45 per cent sulfite). With propene, the pH of these solutions remained constant while 95 per cent of the available sulfite was consumed, and the proportions of sulfonate and sulfate formed corresponded closely to the bisulfite–sulfite ratio (29). It follows that if an alkene reacts sluggishly with bisulfite, the proportion of oxidation increases and a higher proportion of sulfite should be used.

Although the only products isolated from the reaction of bisulfites with simple alkenes are the addition products, there is evidence that some by-products are formed. Kolker and Lapworth (100) observed the formation of variable, but usually very small, proportions of what they thought to be sulfite esters. These by-products were easily oxidized by bromine and permanganate. When hydrolyzed with acid, they yielded sulfur dioxide. By hydrolysis with acid, the formation of small amounts of sulfur dioxide has in some cases been confirmed qualitatively in this laboratory, but since most crude addition products do not reduce iodine (29), the ability of these products to reduce bromine and permanganate is more likely due to unsaturation rather than to the presence of sulfite esters. Attempts have been made, by bromide–bromate titration (105) and by permanganate assay (81), to estimate the degree of unsaturation in the crude sulfonic acids. Since the two methods do not agree and since the existence and proportions of unsaturated sulfonate, hydroxysulfonate, and sulfite esters in the addition products have not yet been demonstrated, the results cannot be considered reliable. In additions to propene (29), about 15 per cent unsaturation in the products is claimed when the buffers are of nearly ideal composition. With more acid or more basic buffers, the yields of sulfonic acids are much lower, but the proportion of unsaturation increases with the acid concentration. In additions to liquid alkenes using oxygen at 1 atm. pressure, 1.5 per cent to 18 per cent unsaturation has been reported in the product. With nitrite instead of oxygen, it was shown conclusively that unsaturation was absent (130). The significance of unsaturation will be considered in the case of styrene, where various reaction products have been isolated and analytical methods have been tested.

The yields of addition products from the less reactive alkenes are decreased by the use of either alcohol or hydrocarbon solvents and slightly increased by the use of ethylenediamine. Since ethylenediamine has little effect in nitrite-promoted additions, it probably serves mostly to inhibit the oxidation of bisulfite (29, 130).

Attempts to add bisulfites to acetylene yielded only traces of unidentified sulfonic acids (29).

C. THE REACTION OF BISULFITES WITH STYRENE

Since the reaction of styrene with bisulfites is fully described in a recent paper (81), the work need be only briefly summarized here. The reactions were carried out under constant oxygen pressure. At 1 atm. of oxygen, sodium and ammonium sulfite–bisulfite mixtures gave 30 per cent or less of organic sulfonates (the remainder of the sulfite being oxidized to sulfate), but yields up to 68 per cent were obtained at lower oxygen pressures. The reaction of styrene was about as sensitive to excess acid and base as the reactions of those aliphatic olefins which are liquids at room temperature.

In the presence of oxygen, the organic sulfonates always consisted of three types of salts. Where sodium salts were used, the final mixture contained about 25 per cent of addition product (I) corresponding to an abnormal addition reaction, 10 per cent of substitution product (II), and 65 per cent of hydroxysulfonate (III):

$$\underset{\text{I}}{C_6H_5CH_2CH_2SO_3Na} \qquad \underset{\text{II}}{C_6H_5CH{=}CHSO_3Na} \qquad \underset{\text{III}}{C_6H_5CHOHCH_2SO_3Na}$$

The proportions of these products varied slightly. Ammonium salts (from ammonia or the methylamines) gave somewhat more substitution product (II) and correspondingly less addition product (I) than sodium salts; ethylene diammonium sulfite gave a higher proportion (82 per cent) of hydroxysulfonate (III). Additions of aqueous sulfurous acid to styrene in the presence of a large excess of dimethylaniline or pyridine gave about 60 per cent yields of total sulfonates. This increase is probably due to the fact that these bases increase the miscibility of bisulfite and hydrocarbon, and that they maintain the pH at a favorable level. Sodium and ammonium nitrites and ammonium persulfate can replace oxygen in promoting the reaction of bisulfite with styrene but they are no more efficient, 30 mole per cent or more of these substances being required for a 15 to 25 per cent yield of total sulfonates. With these oxidizing agents, no unsaturated sulfonate (II) whatever was found, the proportion of both addition product and hydroxysulfonate being increased.

All three types of sulfonates were isolated in the pure state. No one of them is converted into any other under the conditions of the styrene–bisulfite reaction, and all are stable to hot dilute acids and bases. Therefore all three are thought to be primary products.

Since the presence of an oxidizing agent is necessary for the formation of all three sulfonates, and since in all of them the sulfur is attached to the terminal carbon atom, the three reactions are easily correlated by the assumption that the sulfonate-ion radical formed by reactions 22 and 23 is an intermediate common to all. If such is the fact, then the low yields of addition product (I) prove that only a small proportion of the sulfonate-ion radicals formed undergo reaction 24, whereas the large amount of oxidizing agent consumed in the styrene reaction suggests that this agent reacts with the sulfonate-ion radical. The unsaturated sulfonate may be formed through reaction 25, oxygen being the only oxidizing agent known to give this result:

$$R\underset{\bullet}{C}HCH_2SO_3^- + O_2 \rightarrow RCH{=}CHSO_3^- + HO_2\bullet \qquad (25)$$

The $HO_2\bullet$ radical may react with bisulfite. The hydroxysulfonate (III) is formed in the presence of oxygen, nitrite, or persulfate:

$$R\underset{\bullet}{C}HCH_2SO_3^- + \text{oxidant} \rightarrow R\underset{+}{C}HCH_2SO_3^- + \text{oxidant}^- \qquad (26)$$

$$R\underset{+}{C}HCH_2SO_3^- + H_2O \rightarrow RCHOHCH_2SO_3^- + H^+ \qquad (27)$$

The difference between styrene and the alkenes apparently lies in the ease with which the sulfonate-ion radical reacts with bisulfite (reaction 24). The aliphatic free radicals apparently need little or no activation energy in order to undergo this reaction, and since the concentration of bisulfite is much higher than that of oxygen, the simple alkenes give long chains. The substituted benzyl radical formed from styrene obviously reacts sluggishly with bisulfite, but much more easily with oxygen, considering the low concentration of the latter in solution. If the slow reaction of bisulfite with the substituted benzyl radical is due to the stabilization of the latter by resonance, then this stabilization has little or no effect on the ability of the radical to react with oxidizing agents.

Except for compounds containing carbonyl groups, cinnamyl alcohol seems to be the only styrene derivative whose reaction with bisulfite has been investigated. The reaction depends upon the presence of oxygen (75), but no products have been identified.

V. The Peroxide Effect in Rearrangements

A. REARRANGEMENT OF 1-BROMO-2-BUTENE AND 3-BROMO-1-BUTENE

The peroxide effect in the rearrangement of 1-bromo-2-butene and 3-bromo-1-butene was discovered (66) during a study of the addition of hydrogen bromide to butadiene, of which the bromides in question are the two addition products:

$$CH_2{=}CHCH{=}CH_2 + HX \begin{array}{l} \nearrow XCH_2CH{=}CHCH_3 \text{ ("crotyl halide", IV)} \quad (28) \\ \searrow CH_2{=}CHCHXCH_3 \text{ ("secondary halide", V)} \quad (29) \end{array}$$

It was shown by Winstein and Young (166) that either bromide when pure undergoes, on standing at room temperature, an allylic rearrangement to an equilibrium mixture of 85 per cent crotyl bromide (IV) and 15 per cent secondary bromide (V). Later, it was shown in this laboratory (66) that under the combined influence of hydrogen bromide and ascaridole, rearrangement, even at −12°C., is rapid and complete. Under the same conditions, ascaridole alone has no effect; hydrogen bromide alone causes only slight rearrangement. Young and Nozaki (169) have since employed hydrogen bromide and benzoyl peroxide to accelerate these rearrangements, but the reviewers know of no other application of the early finding. The rearrangements of some homologs of these bromides are reported to be highly susceptible to the effects of traces of unspecified catalysts (170). It is probable that the peroxide effect is widespread in allylic rearrangements of bromides, and that therefore the additions of hydrogen bromide and bromine to conjugated systems need reinvestigation.

That the allylic rearrangement sometimes has a molecular or ionic mechanism is shown by a study of the behavior of 1-chloro-2-butene (IV) and 3-chloro-1-butene (V) (71). As expected, peroxides and air have no effect on their rearrangements, which are very slow except in the presence of a catalyst. Small amounts of anhydrous ferric chloride or of a mixture of cuprous and hydrogen chlorides cause isomerization of either chloride to an equilibrium mixture containing about equal proportions of each isomer. This isomerization is rapid with the former reagent, somewhat slower with the latter. A large proportion of hydrogen chloride alone causes slow rearrangement to a different equilibrium mixture, indicating that this acid forms a complex with one or both of the organic halides. These phenomena show that the rearrangements of these chlorides have much in common with the normal addition of halogen acids to alkenes.

The facts that small amounts of both hydrogen bromide and peroxides are required for a very rapid rearrangement of bromides, and that allyl-type chlorides are not susceptible to corresponding influences, suggest that the peroxide-catalyzed rearrangement of bromides proceeds by a chain mechanism involving bromine atoms or free radicals. On this meagre basis, two such mechanisms are tentatively suggested:

$$\mathrm{CH_2{=}CHCHBrCH_3 + Br\cdot \rightleftarrows CH_2Br\underset{\bullet}{C}HCHBrCH_3 \rightleftarrows CH_2BrCH{=}CHCH_3 + Br\cdot} \qquad (30)$$

$$\mathrm{CH_2C{=}H\underset{\bullet}{C}HCH_3\ (indistinguishable\ from\ \underset{\bullet}{C}H_2CH{=}CHCH_3) + CH_2BrCH{=}CHCH_3 \rightleftarrows CH_2{=}CHCHBrCH_3 + \underset{\bullet}{C}H_2CH{=}CHCH_3} \qquad (31)$$

There are two difficulties with the first mechanism. One is that in the addition of a bromine atom to 1-bromo-2-butene the bromine atom might not attach itself to the 3-carbon atom,[20] as required for rearrangement.

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[20] This difficulty may not arise if it is assumed that the bromine atom adds to the ethylene bond to give the more stable free radical.

The other difficulty is that, wherever a bromine atom adds to either isomer, subsequent separation of a bromine atom from the free radical formed may be too endothermic for a chain reaction. The second mechanism avoids both of these objections. The energy change involved in reaction 31 is very close to zero, and if the exchanges proceed through a chain reaction, the activation energies must also be small. The free radical necessary to start the chain may be formed as follows:

$$\mathrm{CH_2Br\underset{\bullet}{C}HCHBrCH_3}\ (\textit{cf.}\ \text{reaction 30}) + \mathrm{CH_2BrCH{=}CHCH_3} \rightarrow \mathrm{CH_2BrCHBrCHBrCH_3} + \bullet\mathrm{CH_2CH{=}CHCH_3} \quad (32)$$

The conditions for the rearrangement of the products having been established, the addition of hydrogen chloride and hydrogen bromide to butadiene may be considered. As mentioned in the discussion accompanying table 1, the addition of hydrogen chloride to butadiene gives, over a wide range of temperatures (71), 75 to 80 per cent of secondary chloride (V) and 20 to 25 per cent of crotyl chloride (IV). Isomerization of the products under the conditions of addition is negligible. Addition of hydrogen bromide under conditions most favorable for the normal addition (presence of an antioxidant, absence of air, temperature −78°C.) gives within experimental error the same proportion of isomers. As the temperature of addition is raised to 25°C., the proportion of crotyl bromide formed increases to 56 per cent. If the addition is carried out in the presence of a peroxide, only 40 to 45 per cent of crotyl bromide is formed at −78°C., but 70 to 80 per cent of this bromide (approximately the equilibrium mixture) is formed at −12°C.

Since the addition of hydrogen chloride shows no temperature effect, and since at low temperatures in the presence of antioxidants essentially the same results are obtained with hydrogen bromide, it is concluded that the normal addition of a halogen acid to 1,3-butadiene gives about 80 per cent 1,2-addition and 20 per cent 1,4-addition. In additions of hydrogen bromide at room temperature, or in the presence of peroxides, some or all of the additional crotyl bromide found is due to isomerization of secondary bromide first formed by 1,2-addition. The possibility that addition by an abnormal mechanism increases the proportion of direct 1,4-addition has not been ruled out, but the failure to find any 4-bromo-1-butene excludes the possibility that appreciable abnormal 1,2-addition has occurred in any experiment made to date.

B. REARRANGEMENT OF α-BROMOACETOACETIC ESTERS

It has been shown by Hantzsch and coworkers (33) that α-bromoacetoacetic ester rearranges slowly at room temperature to γ-bromoacetoacetic ester, that this change is accelerated by hydrogen bromide, and that it is inhibited by water. However, the α-bromo ester, in spite of its instability at room temperature, can be distilled four or five times *in vacuo* at 100°C. without change. The effect of hydrogen bromide explains the differences between the methods for preparing the two esters directly (21). When acetoacetic ester is brominated in the presence of ice and water, pure α-bromo ester is immediately obtained. When slow bromination lasting several hours takes place in carbon disulfide solution, the γ-bromo ester is formed. If, in the latter preparation, hydrogen bromide is removed by intermittent washings with water, mixtures are obtained. This result suggests that the γ-bromo ester is formed by rearrangement of the α-bromo ester. The α- and γ-bromo derivatives of methyl α-methylacetoacetate have been similarly prepared. Ethyl α-chloroacetoacetate has no tendency to rearrange, even in the presence of hydrogen chloride (21). This difference between the α-chloro and α-bromo esters suggested the possibility of a peroxide effect in the rearrangement of the bromo esters.

By a series of experiments, each lasting only a few hours and carried out in glacial acetic acid solution, it was found that air, a peroxide, or light greatly accelerated the rate of rearrangement of the α-bromo ester by hydrogen bromide (68). In the absence of hydrogen bromide, no rearrangement took place in the presence of a peroxide and light, either with or without hydrogen chloride. In glacial acetic acid, the bromination of ethyl acetoacetate in the absence of air, peroxides, and light gave more than 90 per cent α-bromo ester; in the presence of any one of these agents, 80 per cent or more of the γ-isomer was formed. The bromination of ethyl α-methylacetoacetate was very similar, except that rearrangement was more rapid.

The effects of oxygen, peroxides, and light on the rearrangement of α-bromoacetoacetic esters by hydrogen bromide and the stability of the corresponding chloro esters suggest that the rearrangement has much in common with the rearrangements of the butenyl halides and the addition of hydrogen bromide to alkenes. Probably a part, if not all, of the rearrangement takes place through a chain mechanism in some stage of which bromine atoms are involved. Stability of the bromo esters in the presence of a suitable inhibitor would indicate whether the isomerization is exclusively a chain reaction and whether the chain carrier is the same as in the abnormal addition of hydrogen bromide to alkenes. Such experiments have not yet been performed; consequently any discussion of a mechanism is admittedly speculative. Only in order to show that a simple chain can be written is the following mechanism ventured:

$$\bullet\mathrm{CH_2COCH_2COOC_2H_5} + \mathrm{CH_3COCHBrCOOC_2H_5} \rightleftarrows \mathrm{CH_2BrCOCH_2COOC_2H_5} + \mathrm{CH_3CO}\underset{\bullet}{\mathrm{C}}\mathrm{HCOOC_2H_5} \qquad (33)$$

$$\mathrm{CH_3CO}\underset{\bullet}{\mathrm{C}}\mathrm{HCOOC_2H_5} \rightleftarrows \bullet\mathrm{CH_2COCH_2COOC_2H_5} \qquad (34)$$

The mode of formation of bromine atoms has been indicated in an earlier section. These atoms may attack ester molecules to yield the free radicals necessary to start chains. Since the bromination of acetoacetic ester is reversible, the bromine atoms may attack a bromo ester molecule to give either bromine or hydrogen bromide. Like the second mechanism proposed for the rearrangement of the butenyl bromides, the chain here suggested consists of the transfer of bromine atoms from a molecule to a radical; the chain carrier is not a bromine atom, but a radical which can isomerize. Whatever the mechanism of the rearrangement, the product should be an equilibrium mixture of the γ-bromo ester with a small proportion of the α-isomer.

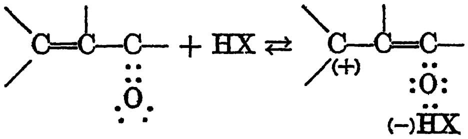
C. CIS–TRANS ISOMERIZATIONS

A thorough discussion of the rearrangement of geometrical isomers is beyond the scope of this review on the peroxide effect. Except for recent work, the subject has been covered by both R. Kuhn (24) and Dufraisse (28). In order that isomerization may occur, the resistance of the double bond to free rotation must be overcome. The assumption by some investigators that all such isomerizations take place by a single mechanism has led to some confusion, for at least four distinct mechanisms will be cited for the conversion of a *cis*-ethylene derivative to its *trans*-form.

The first mechanism is associated with the simplest reaction, represented by the homogeneous, apparently unimolecular, rearrangement of dimethyl maleate in the vapor phase (119, 147). This reaction has a fairly high activation energy and requires a temperature of around 300°C. The uncatalyzed liquid-phase isomerizations of isostilbene and its α-chloro derivatives (149) are also unimolecular. They require a temperature of at least 200°C. and have activation energies of about 35 kg-cal. These isomerizations apparently depend on violent collisions to effect rotation about the double bond.

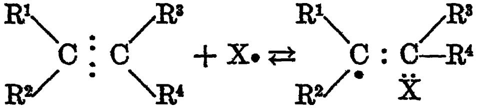
Ultraviolet radiation is known to cause isomerization of ethylene derivatives in the absence of other catalysts. According to Mulliken (118a), absorption of such radiation by an ethylene derivative causes a transition to an excited electronic state in which the perpendicular configuration of the groups placed about the double bond is more stable than the planar configuration characteristic of the unexcited state.

A third type of mechanism is associated with a catalyst which can donate a proton or accept a pair of electrons. Mineral acids (24, 28, 137, 138, 149) are known to be effective in many instances and ineffective in others; primary and secondary, but not tertiary, amines rapidly isomerize dimethyl maleate (18); aluminum, ferric, and zinc chlorides have been effective with the same ester (26); boron trifluoride has been found to rearrange isostilbene, but not dimethyl maleate (127). Various workers have suggested that one of the doubly bound carbon atoms shares a pair of electrons with the catalyst, leaving the other previously doubly bound carbon atom with a positive charge and free to rotate about the axis of the former double bond. After such rotation, dissociation from the catalyst permits reëstablishment of the double bond and consequent formation of the geometrical isomer. If a carbonyl group is conjugated with the double bond, association of the catalyst may take place at the carbonyl group, but then the double bond is shifted and rotation between the carbon atoms previously doubly bound becomes possible:



(35)

Most of the remaining observations on the effects of catalysts suggest that a fourth type of mechanism involves catalysts with two unpaired or an odd number of valence electrons. For the sake of brevity, it will be assumed that all such catalysts act through a single mechanism, although future work may show that this class of substances should be subdivided. The general scheme is represented by reaction 36:



VI VII

(36)

As in the proton-catalyzed mechanism, rotation about the double bond in the intermediate is possible, but the intermediate here is a free radical. Its stability is unknown. The catalysts include univalent atoms, free radicals, molecules with odd electrons, and paramagnetic substances in general. One class of catalysts which has been assumed to function in this manner consists of the alkali metals (24); these cause isomerization without much reaction on the part of the metal. That the isomerization of isostilbene by stilbene disodium (in the absence of free metal) involves free radicals or metal atoms is possible, but doubtful in view of the statement by Ziegler and Wollschitt (171) that isomerization takes place on regeneration of the ethylene compound (after exchange of metal), but not on the appearance of a single free valence. Platinum and palladium blacks have been found to isomerize maleic acid (148) and its methyl ester (24). Paramagnetic metal ions are also said to isomerize the acid (148). The weak effect of oxygen in accelerating both the vapor-phase (147) and liquid-phase (146, 148) isomerizations may be partly due to the paramagnetism of this substance, but in the isomerization of isostilbene (149) the effect of oxygen has been ascribed to the fact that it causes the formation of catalytically active acids. Since nitrogen oxides (24, 27, 146) are better catalysts than oxygen for some isomerizations, the probability that they function through a free radical addition product is somewhat greater. A combination of hydrogen sulfide and sulfur dioxide causes isomerization of maleic acid, although neither gas alone is effective. Heating with aqueous bisulfite has caused rearrangement of erucic acid. In both cases the effect has been attributed (24) to the colloidal sulfur formed. More recent work has shown that a combination of aqueous sulfur dioxide and manganese dioxide (120) rearranges maleic acid, its esters, and citraconic acid. In additions of mercaptoacetic acid and glutathione to maleic acid (118), part of the unreacted maleic acid was isomerized to fumaric acid. Glutathione would neither add to, nor rearrange, *cis*-cinnamic acid; hence it was concluded that the sulfhydryl group must be able to add to a double bond in order to cause isomerization. The close analogy between all of of these observations and those on the addition of mercaptans and bisulfites suggests that free radicals (formed as intermediates in the oxidation of bisulfites or hydrogen sulfide by air, peroxides, or manganese dioxide) are the active agents for the observed isomerizations.

This fourth type of mechanism is closely related to the peroxide effect, because halogen atoms can cause the reactions in question. Wachholtz (159) found that the photochemical isomerization of dimethyl maleate by bromine in carbon tetrachloride solution depended only on the quanta absorbed by the bromine, and that quantum yields as high as 600 were obtained. The isomerization was thought to proceed according to reaction 36, but an exchange of bromine atoms between the free radicals (VII) and the unsaturated molecules (VI) seems more likely than a dissociation. Even higher conversions were obtained when bromine atoms, the presumably active agents, were generated by chemical means (160). In water solution, the action of ferrous sulfate on bromine, hypobromous acid, or bromic acid isomerized 10,000, 1000, and 500 molecules, respectively, of maleic acid per atom of bromine formed. Iodine in the light (24, 28) and at elevated temperatures (167) has been found to catalyze other isomerizations; here iodine atoms seem to be the active agent.

Since it is well established (24, 37) that bromine atoms can cause *cis-trans* isomerizations proceeding through chain reactions, the fact that hydrogen bromide can cause similar isomerizations under conditions favorable for previously described peroxide effects is strong support for the contention that, where hydrogen bromide is thus effective, bromine atoms are involved. The peroxide effect in the rearrangement of geometrical isomers was observed in this laboratory in 1937, but only the first portion of this work has yet appeared. Urushibara and Sinamura have subsequently published several papers in this field; their observations agree with, and extend, those made here. The following description is intended to bring out the relations indicated above and to show how the principal mechanism of isomerization changes with the structure of the unsaturated compound.

In the absence of air and light, the isomerization of stilbene (93, 67, 150) by hydrogen bromide or hydrogen chloride in benzene solution is very slow, requiring several days. The isomerization by hydrogen bromide is accelerated by light, air, peroxides, or by reduced iron or nickel. The accelerating effect of these agents can be overcome by catechol, less effectively by diphenylamine. The isomerization by hydrogen chloride is unaffected by light or peroxides. These results show that there is a slow isomerization by acids through a molecular or ionic mechanism, but that the isomerization by hydrogen bromide proceeds through a much more rapid chain mechanism. That this chain mechanism involves bromine atoms is suggested by the known ability of such atoms to cause isomerizations, together with the fact that small proportions of stilbene dibromide are formed as a result of the oxidation of hydrogen bromide in the presence of air and light (93, 150). α,α-Dichlorostilbene is isomerized by a combination of hydrogen bromide and oxygen, but not by halogen acids alone (149).

In the isomerization of maleic acid and some of its derivatives when the halogen acids are present, rearrangement by the bromine-atom chain mechanism is negligible compared with that by the ionic or molecular mechanism. Sinamura (137) found that the isomerization of dimethyl maleate by hydrogen bromide is unaffected by oxygen or antioxidants and that hydrogen chloride is nearly as effective as hydrogen bromide in producing the reaction. Kharasch, Mansfield, and Mayo (93) found that isomerization of maleic acid, maleic ester, and bromomaleic acid in air was catalyzed to about the same extent by both hydrogen bromide and hydrogen chloride.

Further work by Sinamura (138) shows that the behavior of methyl allocinnamate is intermediate between that of maleic ester and stilbene with respect to both mechanisms. With this compound, hydrogen chloride is distinctly less effective than hydrogen bromide, and the isomerization by hydrogen bromide is only moderately accelerated by oxygen or partially inhibited by catechol. Work in this laboratory (93) shows that isomerization of the labile form of α-phenylcinnamic acid to the stable form by hydrogen bromide is accelerated by air and light, whereas the apparently slower isomerization by hydrogen chloride is not.

From the foregoing discussion it seems probable that acids usually cause isomerization of a *cis*- to a *trans*-ethylene derivative. This mechanism is most important when the ethylene bond is conjugated with one or more carbonyl groups. Probably any type of ethylene derivative can also isomerize by the atom or radical type of mechanism. Examples of the isomerization of maleic acid derivatives by the bromine-atom mechanism have been cited, but two groups of workers have failed to observe any evidence of this mechanism in the presence of hydrogen bromide. It may therefore be concluded tentatively that, with maleic acid derivatives, the action of hydrogen bromide or hydrogen chloride through the polar mechanism is large compared with the action of the former reagent through the atom mechanism. The reverse is true for isostilbene, whereas the behavior of allocinnamic ester is intermediate.

Such considerations show also that the varying effectiveness of different reagents, which has often in the past been described as anomalous, may easily be fitted into a general scheme. Some *cis*-derivatives should be expected to rearrange easily by several mechanisms, whereas others may rearrange with difficulty by some or all mechanisms. Accordingly, it is not at all surprising that one group of investigators found no correlation between catalytic activity and magnetic susceptibility (26). In the large amount of experimental work required to permit comparisons between different alkenes or different catalysts, it will be necessary to establish the mechanism of each isomerization.

VI. Conclusion

In all the studies discussed in the foregoing review the experimental facts seem to be best explained by the hypothesis that the striking effects of oxygen and peroxides arise out of their ability to initiate chain reactions in which atoms or free radicals act as chain carriers. So-called solvent effects and inhibitory effects of traces of various materials are best interpreted as the result of their effects on chain reactions. Many discrepancies in observations recorded in the earlier literature are explained; many hitherto isolated phenomena are correlated; and many supposed abnormalities are reduced to parts of a logical pattern.

It is perhaps of even greater significance that a new and broader outlook on organic reactions in general is opened up by this hypothesis. The concept of chain reactions in solution, involving atoms or free radicals, will doubtless in many cases supersede earlier limited and inadequate notions which ascribed all reactions to simple unimolecular or bimolecular mechanisms. In any event, it now seems a necessary supplement to such ideas.

Even though future work may necessitate changes in the theoretical concepts of chain reactions, the present ideas have served as a powerful working hypothesis. Already they have been applied in this laboratory to several classes of reactions other than those here discussed. Such applications are the following:

1. The bromination of phenanthrene (72), toluene (73), cyclopropane (78), cyclohexane, methylcyclohexane, isobutane (90), aliphatic acids, acid halides, and anhydrides (91).
2. The use of sulfuryl chloride (in the presence of a peroxide) as a chlorinating agent for aliphatic compounds (79, 82, 86).
3. The use of sulfuryl chloride (under illumination in the presence of pyridine) as a sulfonating agent for aliphatic compounds (80, 89).
4. The introduction of the —COCl group into aliphatic compounds by the use of a peroxide and oxalyl chloride (92), or by the use of light and either oxalyl chloride or phosgene (85).
5. The use of peroxides in accelerating the chlorination of hydrocarbons in the dark (88).

It is hoped that a review of these and related phenomena will be undertaken when sufficient data become available.

The principles discussed in this paper have been developed in collaboration with Prof. M. S. Kharasch over a period of several years. He has assisted in determining the scope of this review and has offered many helpful criticisms of its content. Dr. James K. Senior has greatly assisted the authors in the revision of the manuscript.

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THE FRIES REACTION

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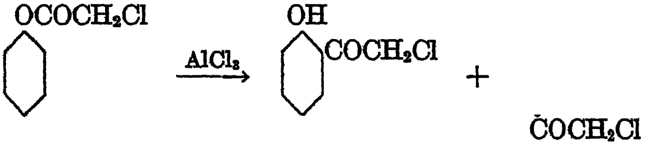
The Fries reaction is the conversion of a phenol ester, on treatment with aluminum chloride, to an *o*- or a *p*-hydroxy ketone or to a mixture of *o*- and *p*-hydroxy ketones. The position, relative to the hydroxyl group, taken by the acyl group depends upon the temperature at which the reaction is run, upon the nature of the acyl group, and upon the structure of the phenol. Low reaction temperatures lead to *p*-hydroxy ketones, while high reaction temperatures lead to *o*-hydroxy ketones. As the size of the acyl group increases,—for aliphatic acyl groups,—the amount of *o*-hydroxy ketone formed increases. Para-substituted phenol esters furnish only *o*-hydroxy ketones. A methyl group in the ortho position in the phenol ester favors the formation of *p*-hydroxy ketones, while the same group in the meta-position favors the formation of *o*-hydroxy ketones. Nitro, acyl, or carboxyl groups in the phenol ester slow up or stop completely the Fries reaction. With certain di- and tri-alkylphenol esters the shift or elimination of alkyl groups has been observed in the Fries reaction. It is suggested that these abnormal reactions are due to the action of aluminum chloride on the normal Fries reaction products. Three mechanisms have been advanced for the Fries reaction: cleavage of the ester by aluminum chloride to form a phenolate and an acid chloride and acylation of the phenolate by the acid chloride; acylation of one molecule of a phenol ester by a second molecule; and a true intramolecular rearrangement without the intervention of normal valence compounds as intermediates. Evidence has been advanced to show that the reaction can proceed by any of these paths, but there is as yet no evidence which establishes any one or ones as the actual path. With those *p*-hydroxy ketones having a substituent ortho to the acyl group, a reversed Fries reaction, leading to the formation of a phenol ester, has been observed.

I. INTRODUCTION

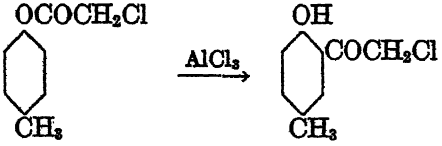
The Fries reaction is an exceedingly convenient and general method for preparing phenol ketones from phenol esters. There is available in the chemical journals a large amount of information on the techniques for effecting the Fries reaction, on the generality and limitations of the reaction, and on the mechanism of the reaction. This information has never been made available in one place and it is necessary, in order to use the Fries reaction to full advantage in preparative work, to make a fairly complete survey of the original articles,—a survey which is time-consuming because of the number of articles, the mass of facts which they contain, and the contradictions with which they abound. The writer had occasion to make such a survey for his own use; it is presented here for others who may find it useful.

Before discussing the Fries reaction proper it is desirable to distinguish between it and the Friedel–Crafts reaction, of which it is essentially a minor variant. The basis for the distinction is that in the Friedel–Crafts reaction for the preparation of phenol ketones a phenol is treated with an acid chloride and aluminum chloride, while in the Fries reaction a phenol ester is treated with aluminum chloride. This may appear at first glance a perfect example of the academic distinction without a difference for, almost without exception, the same product can be prepared using either the Friedel–Crafts or the Fries reaction and it is, of course, true that phenols and acid chlorides react to form phenol esters. However, the distinction between the two reactions has a valid practical basis, for the Fries reaction usually gives much better results (18, 53, 60).

The Fries reaction was discovered in a successful attempt to avoid the difficulties encountered in preparing certain phenol ketones by the Friedel–Crafts reaction. Fries was seeking a method of preparing *o*-chloroacetyl phenols for use in synthesizing coumaranones. The reaction between phenols, chloroacetyl chloride, and aluminum chloride was not satisfactory since, often, two chloroacetyl groups were introduced into the phenols. Fries, therefore, heated phenyl chloroacetate (I) with aluminum chloride and obtained a mixture of *o*-(chloroacetyl)phenol (II) and *p*-(chloroacetyl)-phenol (III). From *p*-cresyl chloroacetate (IV) on similar treatment the sole product was the *o*-hydroxy ketone (V) (27, 28).

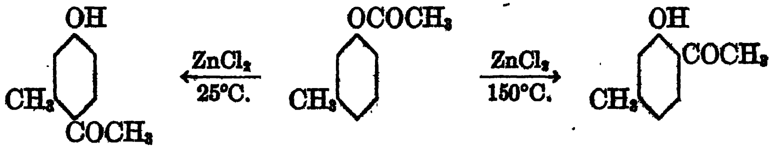


I II III



IV V

Four years prior to Fries' first publication, Eykmann (23, 24) had shown that *m*-cresol and acetyl chloride when treated with zinc chloride furnished, at the ordinary temperature, 2-methyl-4-hydroxyacetophenone (VI) and, at higher temperatures, 2-hydroxy-4-methylacetophenone (VII). This was the first indication of the extremely important influence of the reaction temperature on the position taken by the acyl group. Eykmann used the crude reaction product obtained from *m*-cresol and acetyl chloride without isolating *m*-cresyl acetate.



VI VII

Another important factor in the Fries reaction, the use of nitrobenzene as a solvent, was indicated even earlier by Behn (14), who patented in 1897 a procedure for preparing phenol ketones by treating phenols and acid chlorides in nitrobenzene solution with aluminum chloride. And finally, going still earlier, Döbner (22) in 1881 prepared phenyl benzoate and, without purifying the crude ester, heated it with benzoyl chloride and aluminum chloride to obtain the benzoate of *p*-hydroxybenzophenone.

II. TECHNIQUES

By far the most important single article on the technique of the Fries reaction is that by Rosenmund and Schnurr (52). These authors showed that earlier workers had used too drastic conditions for the reaction and had unnecessarily prolonged the time of reaction. They developed two general procedures, the first for preparing *p*-hydroxy ketones and the second for preparing *o*-hydroxy ketones. In both procedures 1 mole of aluminum chloride is required to convert 1 mole of a phenol ester to a hydroxy ketone (compare, however, the guaiacol esters on page 426). Using technical aluminum chloride it is advisable to employ up to a 25 per cent excess in order to allow for inert ingredients.

The preparation of *p*-hydroxy ketones is based on Behn's patent (14): a solution of a phenol ester and aluminum chloride in nitrobenzene is kept for 24 hr. at room temperature or for 1 hr. at 60°C. The use of nitrobenzene reduces by 80° to 100°C. the temperature necessary for the reaction to proceed at a useful rate (compare reference 13). The importance of this will be seen when the effect of temperature on the course of the reaction is considered (page 417). The preparation of *o*-hydroxy ketones requires higher temperatures, and the preferred procedure consists in heating an intimate mixture of a phenol ester and aluminum chloride without a solvent for from 20 to 40 min. at about 140°C.

These generalized procedures work well and give excellent yields of phenol ketones with a variety of phenol esters. It is, of course, advisable with some compounds to modify slightly the reaction times and temperatures just described in order to secure maximum yields, but such modifications are seldom essential. Other techniques have been recommended from time to time, but only a few require mention. Zinc chloride has been used in numerous Fries reactions, but it offers no advantages over aluminum chloride in either convenience or economy. Boron fluoride has been successfully used for the low-temperature reaction leading to *p*-hydroxy ketones (10, 46). Chlorobenzene (60) and tetrachloroethane (15) have been used as solvents in Fries reactions run at high temperatures, instead of heating an ester with aluminum chloride without a solvent. Carbon disulfide has been used to ensure complete mixing of the aluminum chloride and ester in reactions where high-temperature heating is to be employed. The reactants are dissolved in carbon disulfide, which is then removed by distillation and the residue is heated to the desired temperature (19, 25, 26).

The claim that phenol esters will undergo a Fries reaction on heating alone (56) has not been confirmed (5).

III. APPLICABILITY

The Fries reaction is of wide applicability, since both the acids and the phenols from which the phenol esters are derived can be varied within extensive limits and since, in many cases, it is possible to prepare at will either an *o*- or a *p*-hydroxy ketone from the same ester. The precise position, relative to the hydroxyl group, which will be taken by the acyl group depends upon the temperature at which the reaction is run, upon the nature of the acyl group, and upon the structure of the phenol. These three factors will be considered in the order in which they have been listed, but a brief summary, first, of the variety of esters which has been used in the Fries reaction will give an idea of the material to be covered.

The acids from which the phenol esters are derived may be aliphatic, aromatic, or mixed aliphatic-aromatic. They may be of low or high molecular weight and saturated or unsaturated. The phenols may be derived from benzene, naphthalene, phenanthrene, biphenyl, or coumarin. Hydroxy derivatives of benzene have been most extensively used, and they have been mono-, di-, or tri-hydroxy compounds. Using monohydroxybenzenes, as long as there is an ortho- or para-position available the presence of a single alkyl group or halogen atom in the nucleus introduces no complications (see, however, pages 417 to 425 for the polyalkylphenols). A nitro or a benzoyl group in either the ortho- or the para-position to the hydroxyl group stops the reaction (52). A carboxyl group or an acetyl group in the ortho-position does not interfere, but either group in the para-position does stop the reaction (19). Attempts to run Fries reactions with acyl derivatives of 3,5-dihydroxybenzoic acid (44) and 1,3,5-triaminobenzene (34) were unsuccessful.

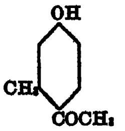
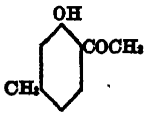
The effect of temperature on the course of the Fries reaction, first observed by Eykmann (23, 24), has been remarked by numerous workers and was examined in detail by Rosenmund and Schnurr (52). Their results with *m*-cresyl acetate are reproduced in table 1.

The obvious conclusion is that low temperatures favor the formation of *p*-hydroxy ketones, while high temperatures favor the formation of *o*-hydroxy ketones, and this conclusion is confirmed by the results with *m*-cresyl benzoate. At 100°C. this ester furnishes exclusively a *p*-hydroxy ketone, while at 165°C. the sole product is an *o*-hydroxy ketone. The temperature effect does not, however, permit the preparation in every case of either an *o*- or a *p*-hydroxy ketone, for the nature of the acyl group and the structure of the phenol also play important rôles in determining the course of the Fries reaction. Rosenmund and Schnurr (52) and later Stoughton (58) showed that *p*-hydroxy ketones on heating with aluminum chloride furnish *o*-hydroxy ketones, and this may be the explanation of the temperature effect. With para-substituted phenols, such as *p*-cresol, the formation of an *o*-hydroxy ketone obviously does not involve a *p*-hydroxy ketone as an intermediate.

TABLE 1

Effect of temperature on the Fries reaction

(In each experiment 10 g. of *m*-cresyl acetate was used)

TEMPERATURE	*p*-HYDROXY KETONE  	*o*-HYDROXY KETONE 
°C.	*grams*	*grams*
25	8.0	0.0
50	8.4	0.1
75	8.8	0.2
100	3.7	6.0
120	2.7	7.0
150	1.0	8.0
165	0.0	9.5

The influence of the acyl group in the phenol ester on the course of the Fries reaction must now be considered. First, there are striking differences in the rates with which different acyl groups shift from oxygen to the nucleus. For example, in nitrobenzene solution at 20°C., thymyl acetate undergoes 60 per cent conversion to thymyl methyl ketone in 5 hr. Under the same conditions thymyl benzoate undergoes only 4 per cent conversion to the corresponding phenyl ketone. From observations of this sort the various acyl groups have been arranged in the following order of decreasing rates of shift (52):

$$C_nH_{2n+1}CO \text{ (where } n = 1 \ldots 5) > C_6H_5CH_2CO > C_6H_5CH_2CH_2CO > C_6H_5CH{=}CHCO > C_6H_5CO$$

No differences were observed between benzoyl and substituted benzoyl groups. The same comparative order holds whether the groups shift to the para- or the ortho-position relative to the hydroxyl group. The importance of this series in setting limits to the usefulness of the Fries reaction is twofold. With certain acyl groups the rate of shift to the para-position is so slow that the preparation of *p*-hydroxy ketones is impracticable; attempts to increase the rate of para conversion by increasing the temperature are futile, for they result instead in the formation of *o*-hydroxy ketones. Examples are furnished by the esters of α-naphthol, which are considered later (page 427). With other acyl groups the conversion to *p*-hydroxy ketones is practicable, but the temperatures required for the formation of *o*-hydroxy ketones are so high that the material is destroyed in the process. *p*-Cresyl cinnamate, which cannot be converted to 2-hydroxy-5-methylbenzalacetophenone, offers an illustration.

TABLE 2

Effect of the size of the acyl group on the product formed

ESTER	REACTION TEMPERATURE	YIELD OF *o*-HYDROXY KETONE
	°C.	*per cent*
m-Cresyl propionate	25	67
	2	65
m-Cresyl butyrate	25	66
	2	72
m-Cresyl valerate	25	67
m-Cresyl caproate	25	62

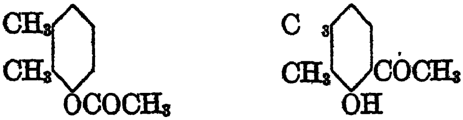
The size of the acyl group is also of importance in determining whether an *o*- or a *p*-hydroxy ketone will be formed in a Fries reaction. This factor was discovered by Coulthard, Marshall, and Pyman (17), and studied in detail by Baltzly and Bass (12; compare also 31). The latter workers examined a series of esters of *m*-cresol and aliphatic acids. Only the acetate furnished a *p*-hydroxy ketone as the principal product. With all the other esters the principal product was an *o*-hydroxy ketone, even when the reaction was run at low temperatures. A selection from the data of Baltzly and Bass, given in table 2, is illustrative.

These results do not contradict those of Rosenmund and Schnurr with *m*-cresyl acetate given in table 1, but they do make questionable any generalization from that data as to the decisiveness of the temperature effect in the Fries reaction. Baltzly and Bass concluded that the temperature at which the reaction is run and the structure of the phenol are the primary factors determining the course of a Fries reaction but that, when these factors counterbalance, the size of the acyl group will control the course of the reaction. Additional information on this question, using esters of other phenols than *m*-cresol, would be desirable. At present we are in the rather awkward situation of having two generalizations, each of which limits the other and neither of which is of sufficient generality to inspire confidence.

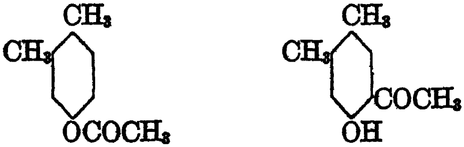
The third factor in determining the course of the Fries reaction, the structure of the phenol from which the phenol ester is derived, remains now to be considered. When esters of phenol and the three cresols are employed the reaction takes place without complications. *p*-Cresyl esters and esters of other para-substituted phenols furnish only *o*-hydroxy ketones. This fact and the relatively high temperature required for the ortho shift account for certain apparently anomalous statements in the original literature. For example, it is reported (36) that *p*-cresol, benzoyl chloride, and aluminum chloride furnish *p*-cresyl benzoate and not 2-hydroxy-5-methylbenzophenone. The reaction reported was not run at a sufficiently high temperature to bring about formation of the *o*-hydroxy ketone. Esters of *o*-cresol furnish only *p*-hydroxy ketones, while aliphatic esters of *m*-cresol, with the exception of the acetate, furnish only *o*-hydroxy ketones. The effect of a methyl group ortho or meta to the phenolic hydroxyl, leading in the former case to the formation of *p*-hydroxy ketones and in the latter case to the formation of *o*-hydroxy ketones, is probably general for other alkyl groups.

A considerable number of esters of di- and tri-alkylphenols have been examined, principally by Auwers and his associates. Certain of these were esters of 2,4,6-trialkylphenols, so that the migration or elimination of an alkyl group was necessary in order for the Fries reaction to take place. Other trialkylphenol esters and all the dialkylphenol esters contained at least one unsubstituted ortho- or para-position, yet in certain of these compounds an alkyl group was either eliminated or changed its position during the reaction. This shift or elimination of an alkyl group is of importance, for it makes uncertain the structures of the phenol ketones formed in the Fries reaction and thereby seriously decreases the usefulness of the reaction. Consequently it is necessary to examine these abnormal Fries reactions in detail. The most satisfactory procedure is to divide the material into three parts and to consider in order the dialkylphenol esters, the trialkylphenol esters having at least one unsubstituted ortho- or para-position, and the 2,4,6-trialkylphenol esters.

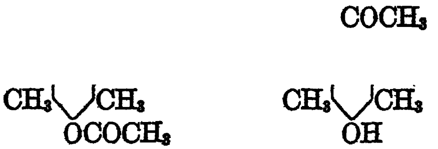
A representative picture of the behavior of the dialkylphenol esters is given by the six xylenyl acetates which were examined by Auwers and his associates.


VIII

(6)


IX

(4)


X

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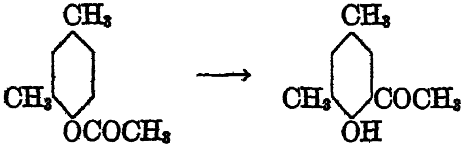
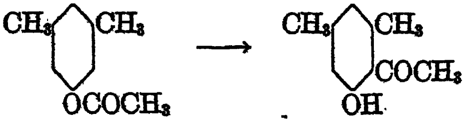
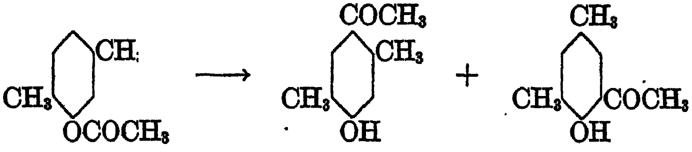

XI

(4)


XII

(1, 2)

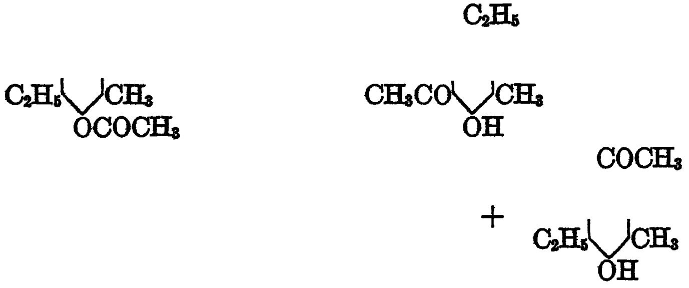

XIII XIV XV (4)

The most striking feature about these results is that with only a single ester (XIII) does an alkyl shift occur. Even with this ester—although in the descriptive portion of the original article only the abnormal product (XV) is mentioned—rearrangement is a distinctly subordinate process. For, in the experimental portion of the article referred to, it is found that *p*-xylenyl acetate (XIII) furnishes the normal product (XIV) in a 70 per cent yield, while the yield of the rearranged product (XV) is only 17 per cent. It is unfortunate that, unless the experimental details in the original article are consulted, the impression given is that the abnormal product is the only product. In the opinion of the present writer the alkyl shift observed with *p*-xylenyl acetate has no direct connection with the Fries reaction. It is, instead, a secondary reaction between the normal product (XIV) and aluminum chloride, a reaction which was encountered as a result of the use of too drastic experimental conditions.

There is considerable evidence in support of the explanation just suggested for the formation of the abnormal product from *p*-xylenyl acetate. The experiments with this ester were reported before Rosenmund and Schnurr's paper (52) on techniques appeared and, after the appearance of that paper, Auwers remarked (8) that the Rosenmund technique was not sufficiently drastic to cause alkyl wandering. The question raidse by the alkyl shift with *p*-xylenyl acetate is subject to an experimental clarification, and it is desirable that this clarification be attempted.

A second striking feature of the experiments with the xylenyl acetates is the large number of *o*-hydroxy ketones obtained. Of course, the acetates (IX and XI) in which the para-position is occupied would be expected to furnish *o*-hydroxy ketones, and the acetate (X) in which both ortho-positions are occupied would be expected to furnish a *p*-hydroxy ketone. Of the three remaining acetates, however, only XIII does yield a *p*-hydroxy ketone. This result may be due to the presence in each of the three acetates (VIII, XII, and XIII) of at least one methyl group meta to the ester group, for such a substituent is known to favor the formation of *o*-hydroxy ketones (compare page 419). It may, however, be due to the high temperature used in the experiments. The behavior of the xylenyl acetates (VIII, XII, and XIII) under mild experimental conditions which should lead to the formation of *p*-hydroxy ketones has apparently never been studied.

The remaining information about the behavior of esters of dialkylphenols in the Fries reaction is summarized in the following equations:



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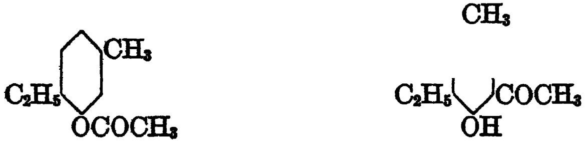

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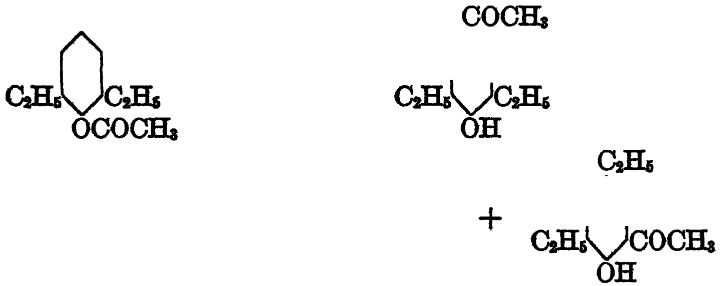

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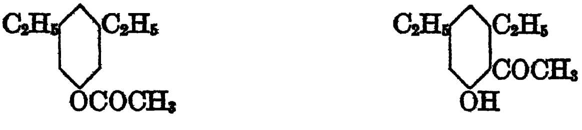

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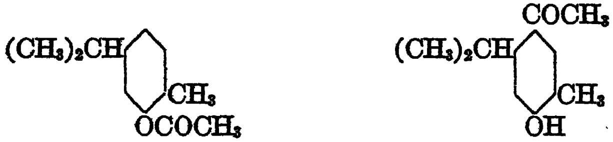
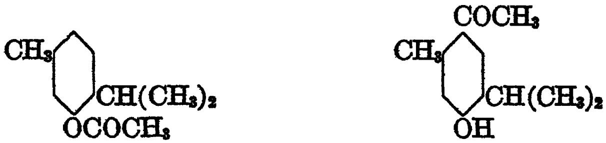


XVI

(52)

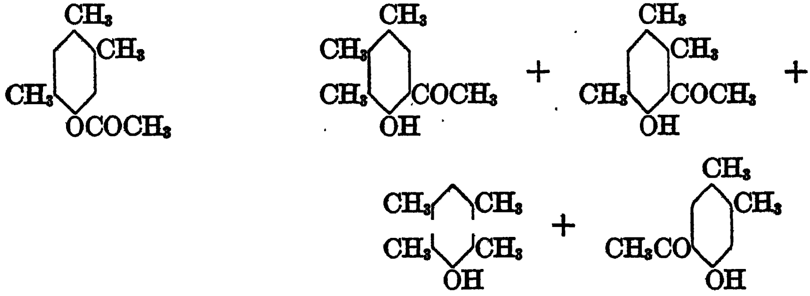


XVII

(23, 52)

Precisely the same comment made about the alkyl shift with *p*-xylenyl acetate applies to these reactions, and that comment receives confirmation from the fact that the two esters, carvacryl acetate (XVI) and thymyl acetate (XVII), which were rearranged using mild experimental conditions behaved normally.

Seven trialkylphenol esters having at least one free ortho- or para-position have been examined by Auwers. The results are shown in the following equations. When more than one product is formed, the principal product is the one immediately following the arrow.



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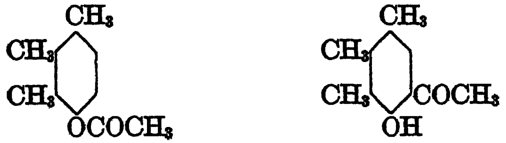

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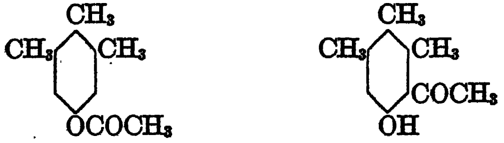

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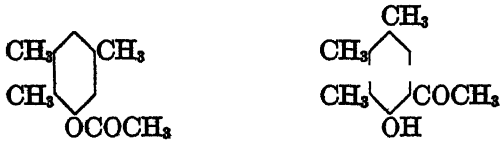

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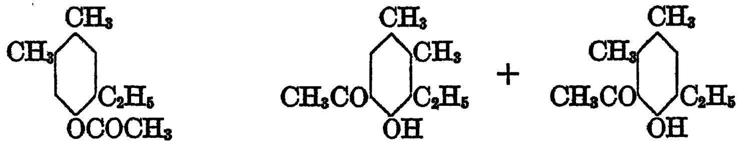

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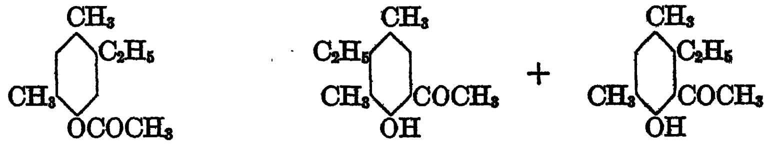

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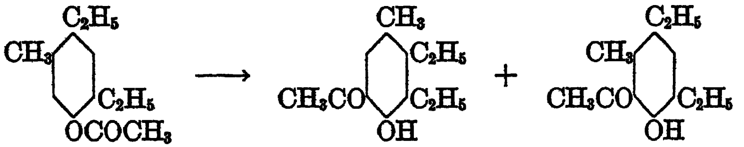
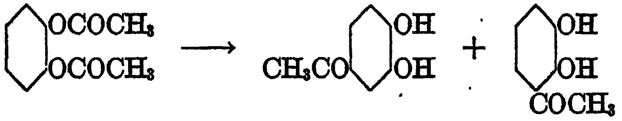

(6)

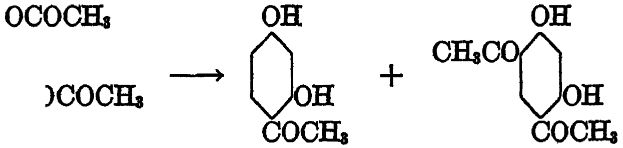
Here alkyl shifts are more common than with the dialkylphenol esters. However, the same question that was raised in connection with the dialkylphenol esters can and should be raised: Are these alkyl shifts an integral part of the Fries reaction, or do they represent a secondary reaction which has taken place between the normal product and aluminum chloride because of the high temperatures used? Again the present writer's opinion is that the second alternative is correct, and there is support for this opinion in the experimental data. Thus, whenever an alkyl shift has occurred, some of the normal product was obtained, indicating that less drastic experimental conditions would furnish more of the normal product. Further, the experimental conditions used were in one instance at least,—that of 2,4,5-trimethylphenyl acetate,—sufficiently severe to bring about alkylation and dealkylation of the type that is known to occur on treating alkylbenzenes with aluminum chloride. It is not our intention to say that every alkylphenol ester with at least one unsubstituted ortho- or para-position will undergo a normal Fries reaction. All the facts are consistent, however, with the view that *p*-hydroxy ketones can and will be formed without alkyl shifts if a suitable experimental technique is used. Whether these *p*-hydroxy ketones can be converted to *o*-hydroxy ketones or whether the direct conversion of esters to *o*-hydroxy ketones can generally be effected without the occurrence of alkyl shifts is much less certain. There is no experimental evidence so far to show that alkyl shifts are an integral part of the Fries reaction.

Auwers and his collaborators (4, 6, 9) have examined the behavior of twenty-two trialkylphenol esters in which the alkyl groups occupy the 2-, 4-, and 6-positions. With these esters the shift or elimination of an alkyl group must occur if a Fries reaction is to take place. The experiments serve to show, therefore, which alkyl groups are most readily displaced and should be discussed with other data on the firmness of attachment of alkyl groups rather than in relation to the Fries reaction. The reader is accordingly referred to the original articles for details.

Our discussion of the Fries reaction with esters of hydroxy derivatives of benzene other than phenol and the alkylphenols will be brief. Esters of the three dihydroxybenzenes have been examined. Hydroquinone diacetate is reported not to undergo a Fries reaction (35). Catechol and resorcinol esters may be converted to the corresponding dihydroxy ketones by the usual technique (38, 50), but a better procedure is to treat an equimolar mixture of the diester and the free phenol with aluminum chloride (51, 53). Improved procedures for preparing acylcatechols have recently appeared (47). Acylresorcinols can so readily be prepared from resorcinol and acid chlorides in a single step that the use of the Fries reaction is superfluous (20). Catechol esters furnish predominantly the 4-acyl derivatives and only secondarily the 3-acyl isomers.

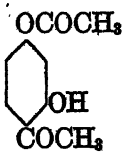


From resorcinol both mono- and di-acyl derivatives may be obtained.

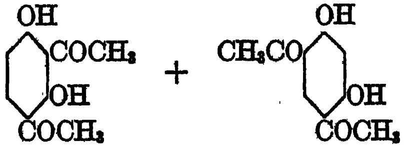


For the preparation of 2-acylresorcinols see page 428.

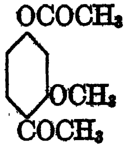
Orientation effects worthy of mention have been observed in Fries reactions with the acetates of 4-acetylresorcinol (XVIII) and its methyl ether (XXI). These substances would be expected to form symmetrical 1,3,4,6-tetrasubstituted products, and the ether (XXI) does furnish such a product (XXII). The hydroxy compound (XVIII), however, furnishes a mixture of 58 per cent of the unsymmetrical (XIX) and 42 per cent of the symmetrical (XX) products. These results have been explained as due to hydrogen bonding in the hydroxy compound (XVIII),—the bonding stabilizing that Kekulé form which leads to the unsymmetrical product (11).



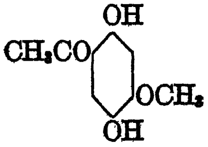
XVIII



XIX XX

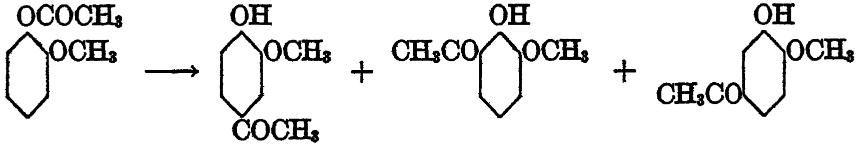


XXI



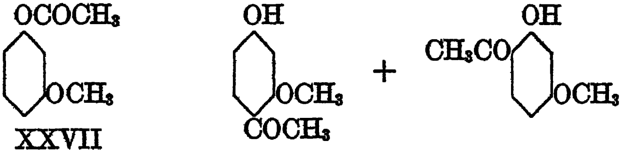
XXII

The acetate of guaiacol (XXIII) has received considerable attention. It illustrates the effectiveness of nitrobenzene in facilitating the Fries reaction. Without a solvent this acetate and aluminum chloride do not react at the ordinary temperature but they do in nitrobenzene solution to furnish apocynin (XXIV) (13). The acetate (XXIII) also requires 2 moles rather than 1 mole of aluminum chloride to bring about reaction (17). One mole of the halide is apparently utilized in complex formation with the methoxyl group.



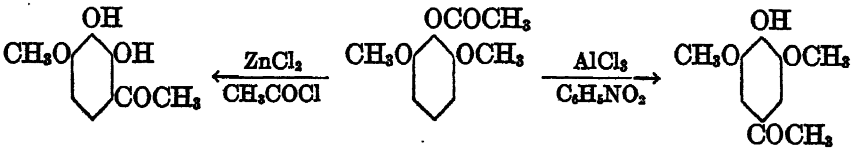
XXIII XXIV XXV XXVI

Reichstein (49) obtained from guaiacol acetate (XXIII) the three products XXIV, XXV, and XXVI. The first two of these are to be expected, but the formation of the third (XXVI) is most unusual, for the shift of an acyl group in a Fries reaction to a position meta to the hydroxyl group is rare. (The diacetate of catechol (see page 425) furnishes some 3-acetylcatechol, but this may be the result of an ortho shift from the 2-position rather than a meta shift from the 1-position.) The Friedel–Crafts reaction with guaiacol and acetyl chloride furnishes the same three products as does the Fries reaction with guaiacol acetate, so the formation of the *m*-hydroxy ketone (XXVI) is not a peculiarity of the Fries reaction. The resorcinol derivative (XXVII), which corresponds to the acetate of guaiacol, yields both an *o*-hydroxy and a *p*-hydroxy ketone but does not yield a *m*-hydroxy ketone (44).

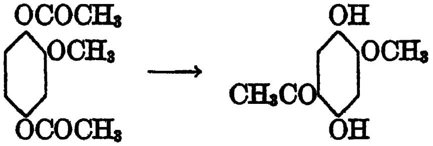


XXVII

Esters of pyrogallol (35), phloroglucinol (33, 35, 45) and 1,2,4-trihydroxybenzene (45) undergo the Fries reaction, and the products are those to be expected. Similarly, esters of various hydroxydimethoxybenzenes and dihydroxymethoxybenzenes have been examined. Generally these esters yield the expected products but one or two unusual results are to be noted, together with the general comment that it would be desirable if the work on this group of compounds were confirmed and amplified. 2,6-Dimethoxyphenyl acetate (XXVIII) with zinc chloride at room temperature in acetyl chloride as a solvent furnishes compound XXIX, the acetyl group taking a meta-position (42). With the same ester and aluminum chloride the acetyl group takes the para-position to yield compound XXX (43).

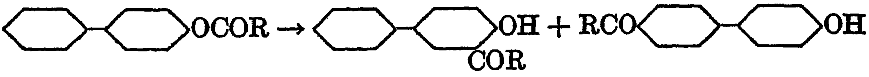

XXIX XXVIII XXX

And, although hydroquinone diacetate does not undergo a Fries reaction, the diacetate of 2-methoxy-1,4-dihydroxybenzene (XXXI) does to furnish compound XXXII (44).


XXXI XXXII

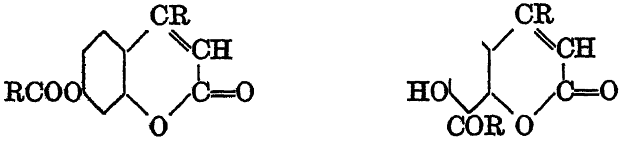
Esters of α- and β-naphthol, of the three hydroxybiphenyls, and of the 2-, 3-, and 9-hydroxyphenanthrenes have been used in the Fries reaction. Esters of α-naphthol furnish 4-acyl-1-naphthols at low temperatures (59, 39, 58). As the size of the acyl group increases, the yields of the 4-acylnaphthols decrease and with certain acyl groups, such as phenylacetyl and benzoyl, the rate of formation of the 4-acyl derivatives is so small that their preparation is impracticable. If the temperature at which the reaction is run is increased, the result is an increase in the amounts of 2-acylnaphthols and 2,4-diacylnaphthols formed. Separate experiments with the 4-acyl-1-naphthols showed that, on heating with aluminum chloride, they were converted to 2-acyl-1-naphthols and 2,4-diacyl-1-naphthols. The failure to recognize the effect of temperature on the course of the reaction and/or the shift of the acyl group from the 4-position in the 4-acyl-1-naphthols led to much confusion in the early literature on the acyl-1-naphthols. β-Naphthyl acetate in the Fries reaction furnishes 1-acetyl-2-naphthol together with 6-acetyl-2-naphthol, the acetyl group entering a different nucleus from that containing the hydroxyl group (59, 29, 30).

The shift of an acyl group to a hydroxyl-free ring, the formation of heteronuclear hydroxy ketones, has also been encountered in the biphenyl series. Aliphatic esters of 2-hydroxybiphenyl are reported to furnish mixtures of 3- and 5-acyl-2-hydroxybiphenyls (3), the yield of the 3-acyl derivatives increasing with the size of the acyl group (31). The structures assigned the hydroxy ketones are reasonable but have never been proved. Esters of 3-hydroxybiphenyl are reported to furnish 4-acyl-3-hydroxybiphenyls (31). Esters of 4-hydroxybiphenyl furnish both the 3-acyl and the 4′-acyl derivatives (15, 32, 25, 26, 16).

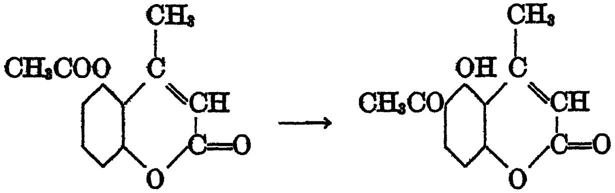


Esters of the 3,4- and 2,5-dihydroxybiphenyls yield tars only (31). In the phenanthrene series, the Fries reaction leads to hydroxy ketones whose structures in certain cases have not been unequivocally established and the reaction offers no advantages over the Friedel–Crafts reaction (48).

Considerable attention has been given the hydroxycoumarin esters and it has been shown that the reaction proceeds normally in this series, leading to the formation of *o*-hydroxy ketones.

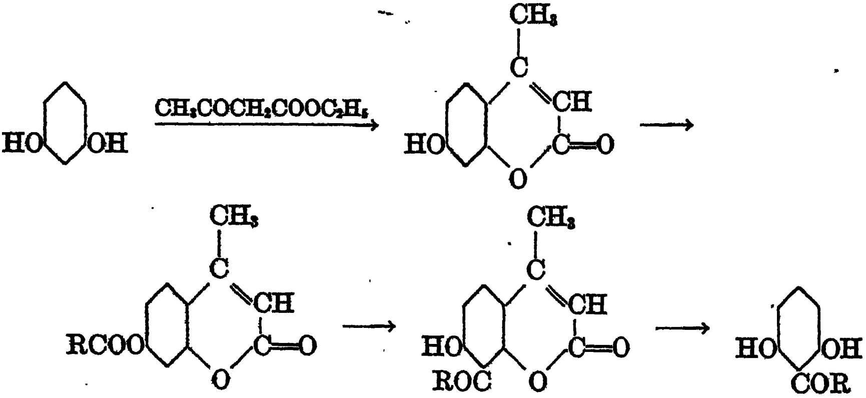


(21, 40, 41)

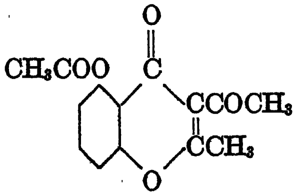


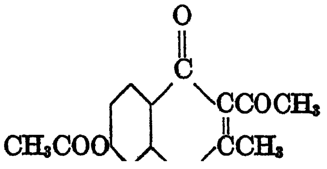
(54)

The importance of the Fries reaction with these materials is that it permits the synthesis of 2-acylresorcinols.



Unsuccessful attempts to carry out Fries reactions have been reported with the following esters (37):

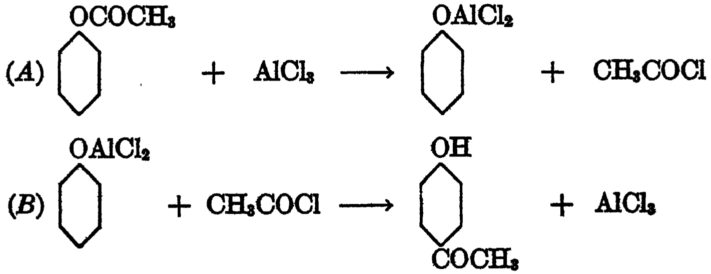




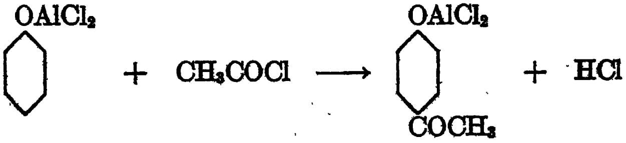
IV. MECHANISM

Three mechanisms for the Fries reaction have received serious consideration and, interestingly enough, while evidence has been presented to show that the reaction can proceed by each of the three proposed mechanisms, there is as yet no decisive evidence in favor of or against any one of the three. This situation, although somewhat unusual, is not too surprising, for when a reagent as powerful as aluminum chloride is used under the conditions of the Fries reaction, many different reactions may and probably do take place, so that the task of proving which one or ones of these alternatives is the reaction path is not easy.

The first mechanism to be considered involves two successive steps: the decomposition of a phenol ester by aluminum chloride to furnish a phenolate and an acid chloride, followed by the nuclear acylation of the phenolate by means of the acid chloride. It is usually represented as follows:

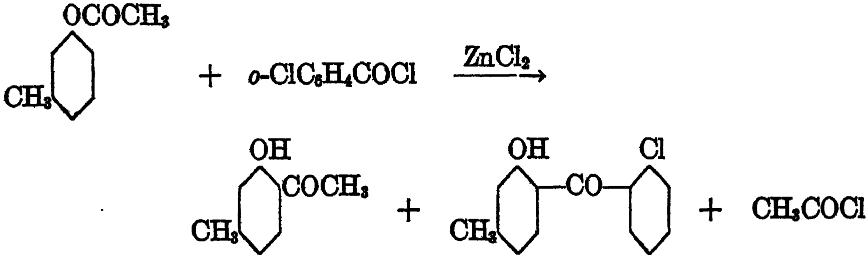


The second step should probably be written



for hydrogen chloride is evolved during the reaction (52).

Skraup and later Cox favored this mechanism and advanced evidence for it. Skraup and Poller (55) heated *m*-cresyl acetate and zinc chloride at 140°C. in a current of hydrogen but failed to isolate the acetyl chloride which they expected according to step *A* above. This failure they explained by the assumption that the acetyl chloride formed was utilized too rapidly in step *B* to permit its isolation. When they heated *m*-cresyl acetate, zinc chloride, and *o*-chlorobenzoyl chloride under the same conditions they were able to isolate small amounts of acetyl chloride and of the benzophenone derivative (XXXIII).



XXXIII

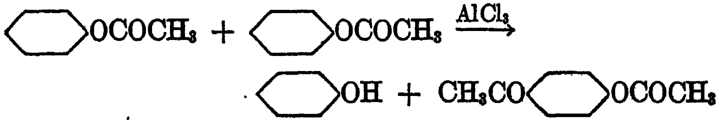
Skraup and Poller felt that this experiment established the mechanism of the Fries reaction. Actually, while the results of the experiment are consistent with the mechanism under discussion, they do not establish that mechanism. Skraup's experiment shows that the Fries reaction can proceed in the way proposed, but it does not show that the reaction does proceed in that way nor does it eliminate alternative reaction paths.

The evidence presented by Cox (19) is from three sources. When Fries reactions are run in diphenyl ether as a solvent, *p*-acyl diphenyl ethers are formed. When the cresyl acetates are rearranged in the presence of absolute alcohol, ethyl acetate is formed. When 2,4,6-trichlorophenyl acetate is heated with aluminum chloride, acetyl chloride is obtained. The same comment made about Skraup's work applies here. This evidence, it seems to the writer, shows that reaction *A*, above, can take place and it shows that the Fries reaction can take place according to the mechanism favored by Skraup and by Cox. It does not, however, show that reaction *A* is a necessary step in the process.

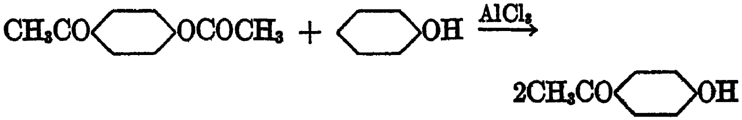
Skraup and Poller (55) also performed some experiments to determine the source of the *o*- and *p*-hydroxy ketones obtained from *m*-cresyl acetate. They found that this ester with zinc chloride at 140°C. gave the *o*-hydroxy ketone, a result consistent with the findings of other workers. They also found that *m*-cresyl acetate did not undergo any reaction when treated with aluminum chloride at room temperature but that if hydrogen chloride was present a Fries reaction took place and both the *o*-and *p*-hydroxy ketones were formed. From the yields of *o*- and *p*-hydroxy ketones in several experiments they concluded that the *o*-hydroxy ketone was the first product and that the *p*-hydroxy ketone was formed from the *o*-hydroxy ketone when hydrogen chloride was present (compare 57). These results should be confirmed, for they contradict completely all the other evidence on this point. There is no other recorded example of the conversion of an *o*- to a *p*-hydroxy ketone, and Skraup and Poller never carried out a direct conversion of this type. An explanation of their results would be possible if one assumed that zinc chloride and aluminum chloride act differently in the Fries reaction (compare the data on the acetate (XXVIII) on page 426), but these results are so strikingly out of line with those of other workers that an attempt to account for them is idle until they have been verified.

The second mechanism for the Fries reaction is that proposed by Rosenmund and Schnurr (52), who suggested that the reaction was bimolecular with one molecule of ester serving to acylate a second molecule.

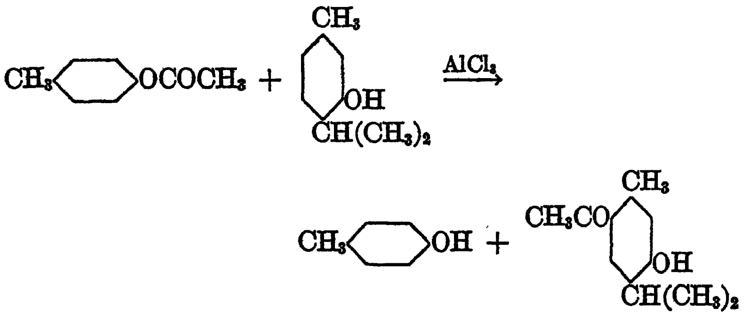
(*C*)



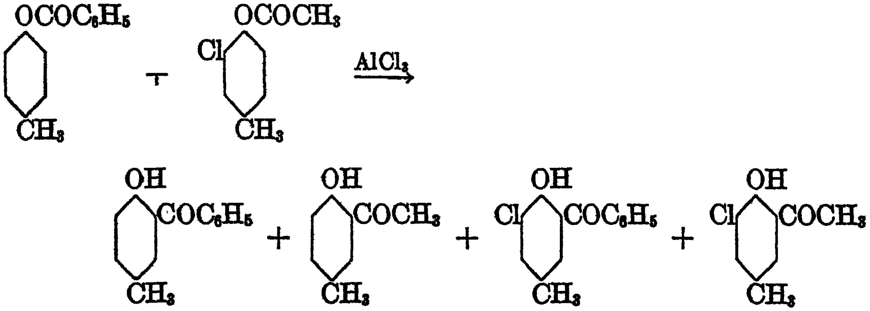
(*D*)



In support of this suggestion Rosenmund and Schnurr showed that when *p*-cresyl acetate in nitrobenzene was treated with aluminum chloride no appreciable reaction took place in 24 hr. at room temperature. If, however, to the reaction mixture just described one equivalent of thymol was added, a 60 per cent yield of thymyl methyl ketone, together with *p*-cresol, was obtained in 8 hr. The explanation given for these results was the following: *p*-Cresyl acetate did not react at room temperature, for the only reaction possible is that leading to an *o*-hydroxy ketone, and the rate of this reaction is negligible under these conditions. Thymol, however, can yield a *p*-hydroxy ketone, and *p*-hydroxy ketones are formed at room temperature. The *p*-cresyl acetate served as the acetylating agent; that is, reaction *C* above took place between two different substances instead of between two molecules of the same substance.

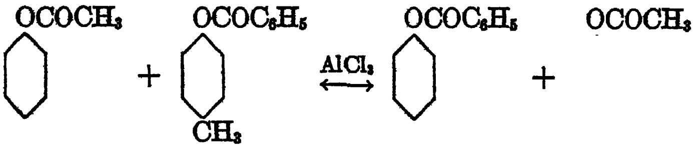


Rosenmund and Schnurr also showed that when a mixture of *p*-cresyl benzoate and 2-chloro-4-methylphenyl acetate was heated with aluminum chloride, all four possible products were formed.

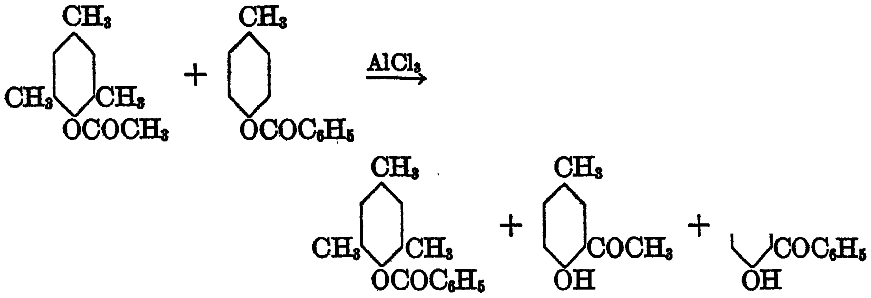


This experiment was interpreted as an example of reaction *C* above. Each ester served to acylate another molecule of the same ester and also to acylate a molecule of the other ester.

It is clear that Rosenmund and Schnurr's results follow very neatly from their mechanism. It must be pointed out that they are explicable equally well on the basis of the first mechanism considered and also as a result of an acyl interchange. Thus if a reaction of the following sort takes place, Rosenmund and Schnurr's experiments lose their significance.

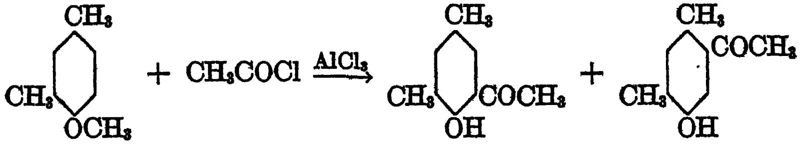


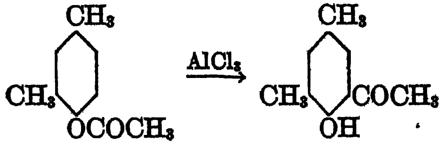
Auwers and Mauss (8) established the occurrence of an acyl interchange when they heated 2,4,6-trimethylphenyl acetate and *p*-cresyl benzoate with aluminum chloride and obtained the three products shown in the equation below.



The situation with respect to Rosenmund and Schnurr's mechanism is then precisely the same as the situation with respect to the first mechanism considered. The Rosenmund and Schnurr mechanism is a perfectly possible one, but there is no evidence which establishes its correctness and eliminates the other alternatives.

The third mechanism, which considers the Fries reaction to be a true intramolecular rearrangement without the intervention of normal valence compounds as intermediates, has been championed principally by Auwers. His argument is that there is a difference in the course of the reaction leading to a hydroxy ketone depending upon whether the acyl group comes from within the reacting molecule (Fries reaction) or from another molecule (Friedel–Crafts reaction). Auwers and Mauss (7, 8) illustrate this with the following typical experiments:

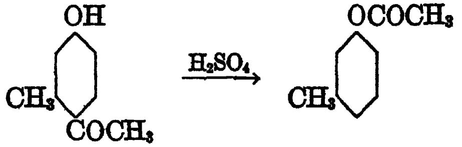




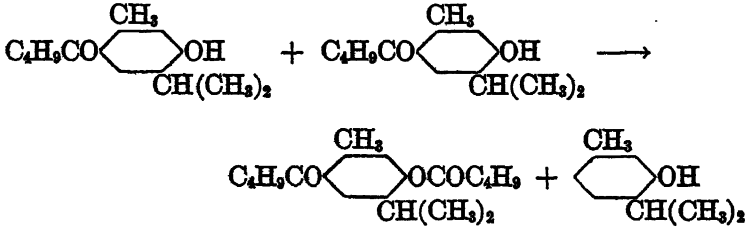
The value of this comparison between two different reactions using different starting materials is difficult to assess. Auwers stresses the statement that, while the Friedel–Crafts reaction with a phenol ether may lead to a *m*-hydroxy ketone, the Fries reaction with a phenol ester always leads to *o*- or *p*-hydroxy ketones. However, the formation of *m*-hydroxy ketones, though rare, is not unknown in the Fries reaction, for guaiacol acetate gives just such a product (49) (compare page 426). The best one can say about the view that the Fries reaction is a true intramolecular rearrangement is the same statement that was made about the other mechanisms,—it has been neither proved nor disproved.

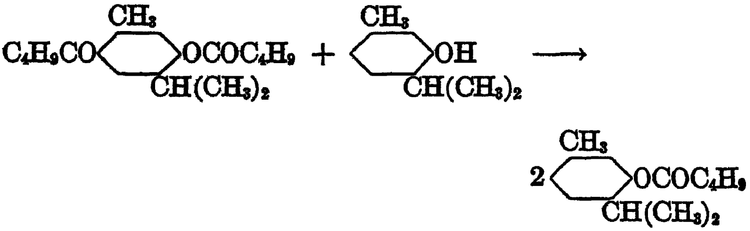
V. REVERSAL OF THE FRIES REACTION

Rosenmund and Schnurr (52) found that with certain *p*-hydroxy ketones the Fries reaction could be reversed, that is, the hydroxy ketones could be converted to phenol esters. The requisites, structural and experimental, for the reverse reaction have been carefully determined. The *p*-hydroxy ketone must contain a substituent ortho to the acyl group and the reversal is effected by heating with sulfuric, camphorsulfonic, or phosphoric acid.

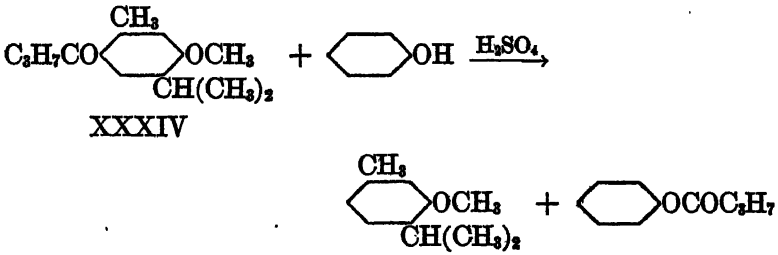


Rosenmund and Schnurr believe that this reverse Fries reaction, like the Fries reaction itself, involves two molecules of the reactants and takes place in two steps. These two steps are the reversal of the two steps (reactions *C* and *D* above) which were suggested for the mechanism of the Fries reaction.

(*E*)


(*F*)


Using the phenol ketone shown in equation *E* it was possible to stop the process at the stage represented by this equation. For when this phenol ketone was heated in high vacuum with the catalyst, thymol was removed as fast as it was formed. Reaction *E* could also be effected between two unlike molecules, for the ketone (XXXIV), which on heating with acid alone is unchanged, reacts as follows when heated with acid and phenol:


XXXIV

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THE OZONIZATION REACTION

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CONTENTS

I. HISTORICAL INTRODUCTION

The addition of ozone to the ethylenic double bond, followed by ozonolysis, the decomposition of the resulting ozonides, has been described recently (47) as the most general and reliable procedure for oxidative cleavage with simultaneous location of the double bond. Although ozone was discovered as early as 1785, its usefulness has been realized only within the last thirty-five years.

The reaction of ozone with organic compounds was first described by Schönbein in 1855 (134). When he bubbled ethylene through water into ozonized air, the bubbles exploded at the surface of the water, and a mixture of carbonic acid, formaldehyde, and formic acid was obtained. Many investigators attempted to apply the method during the next fifty years, but few favorable results were reported. Of the numerous papers which appeared during this fifty-year period, only those of Houzeau and Dieckhoff were important contributions. Houzeau (79) was the first observer to describe the isolation of an ozonide. He obtained, from the treatment of benzene with ozone, a white amorphous product which exploded very readily, yielding a relatively large amount of acetic acid. Dieckhoff (32) carried these experiments a step further by isolating a crystalline product which exploded at 50°C.

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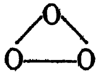
Harries (52) continued this work, and from 1901 to 1916 published ninety-six papers (53) concerning ozone and its reaction with organic substances. These researches covered the entire field of ozonolysis in a comprehensive manner, and resulted in establishing the reaction on a useful basis.

Further investigation has added new knowledge of the mechanism of the reaction, but its complete elucidation still remains for future solution. In 1925, Staudinger (142) made an important contribution to the theory of ozonization, which has been added to in the work of Rieche (126), Pummerer (122), F. G. Fischer (42), and Briner (18). Other advances have been made by F. G. Fischer (40) and Whitmore (152) in the methods of decomposing ozonides. Quantitative studies of rates of ozonization have been undertaken in recent years (23, 115), and, in addition, Briner and his collaborators have made numerous measurements of the physical properties of ozonides, such as the Raman spectra (16), dielectric constant (17), and heat of ozonization (20).

II. THE THEORY OF OZONIZATION

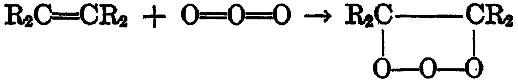
The theoretical treatment of ozonization has received the attention of many investigators, but still remains an unsolved problem. The reaction has, nevertheless, been applied successfully to many questions of structure. The slow development of the theory of ozonization is easily understood when the unstable and explosive nature of the intermediates, the so-called ozonides, is considered. In addition, the course of the reaction is very sensitive to numerous factors, such as the ozone concentration, the duration of ozonization, the temperature of the reaction, the solvent, the concentration of the solution, and, of most importance, the method of decomposition.

In formulating a theory of ozonization, consideration must first be given to the structure of the ozone molecule. Many arrangements of the oxygen atoms have been presented (136), of which the two most commonly considered have been the cyclic structure , in which the three oxygen atoms are bivalent, and the chain formula of Harries, O=O=O, adopted by analogy to that of sulfur dioxide, O=S=O. The pronounced reactivity of one of the three oxygen atoms in the ozone molecule is not accounted for by either of these structures, and a third formula (104, 105), in which only two of the oxygen atoms are linked by a double bond, is currently accepted.

$$:\ddot{O}::\ddot{O}:\ddot{O}:$$

There is in ozone, accordingly, one oxygen atom held by a coördinate valence, which should account for the abnormal reactivity of the molecule. This atom would be repelled easily, would exhibit a tendency to complete its octet, and would facilitate the addition of the molecule to the carbon-to-carbon double bond.

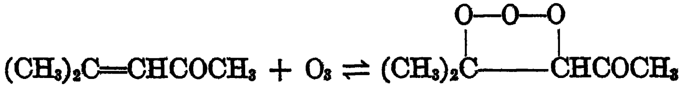
Harries (54) visualized an addition compound as the initial substance arising from the action of ozone on a double bond, analogous to other products of addition to an unsaturated linkage,



$$R_2C{=}CR_2 + O{=}O{=}O \rightarrow \begin{array}{ccc} R_2C & \text{——} & CR_2 \\ | & & | \\ O & \text{—}O\text{—} & O \end{array}$$

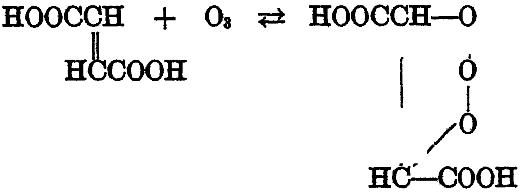
but his experimental evidence was relatively meager.

His proof rested chiefly on two observations: firstly, that mesityl oxide forms an ozonide which, on heating, spontaneously regenerates mesityl oxide (54),



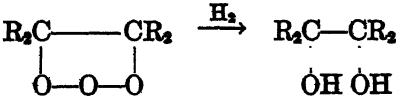
$$(CH_3)_2C{=}CHCOCH_3 + O_3 \rightleftharpoons \begin{array}{ccc} O & \text{—}O\text{—} & O \\ | & & | \\ (CH_3)_2C & \text{——} & CHCOCH_3 \end{array}$$

and that fumaric acid adds ozone loosely and loses it on standing (54).



$$\begin{array}{c} HOOCCH \\ \| \\ HCCOOH \end{array} + O_3 \rightleftharpoons \begin{array}{ll} HOOCCH\text{—}O & \\ | \quad\quad\quad O & \\ | \quad\quad\quad | & \\ \quad\quad\quad\; /O & \\ HC\text{—}COOH & \end{array}$$

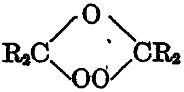
Pummerer (122) and Briner (15) have recently repeated these experiments and have been unable to duplicate Harries' observations. Harries had found, however, that these ozonides, on reduction using all of the methods then known, did not yield either the starting materials or the 1,2-glycols which would be expected according to his formula.



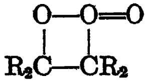
$$\begin{array}{ccc} R_2C & \text{——} & CR_2 \\ | & & | \\ O & \text{—}O\text{—} & O \end{array} \xrightarrow{H_2} \begin{array}{cc} R_2C\text{—} & CR_2 \\ | & | \\ OH & OH \end{array}$$

Pummerer (122) and F. G. Fischer (42) have repeated Harries' reduction of mesityl oxide ozonide, employing the gentlest methods of reduction in the cold, such as the use of hydroquinone, hydrazobenzene, aluminum amalgam, zinc dust plus silver nitrate and hydroquinone as catalysts, and catalytic hydrogenation at 0°C., and have been unable to detect the presence of the glycol in any experiment.

Staudinger (142), in 1925, had stressed the importance of these fundamental objections, and considered his isozonide formula,

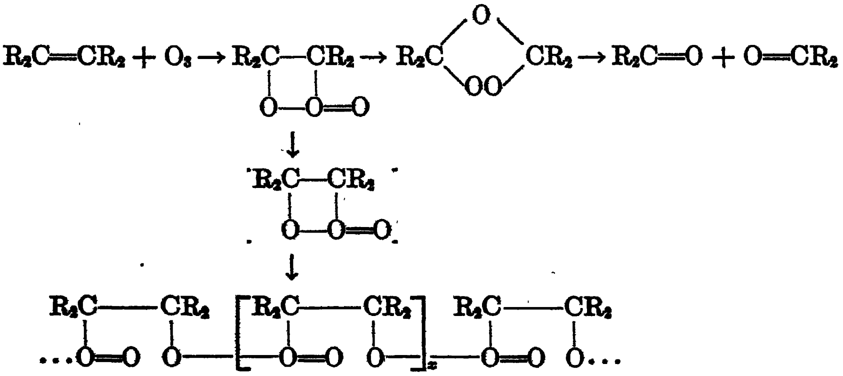


to be correct for most ozonides. Here the carbon chain is already broken, so that only the usual decomposition products would be expected on reduction, and not glycols with intact carbon chains. As primary products of ozonization he assumed the formation of molozonides, to which he assigned the formula,

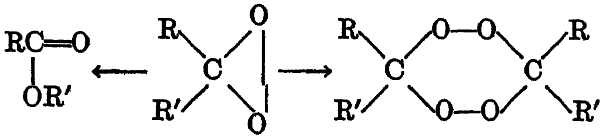


$$\begin{array}{c} O-O=O \\ |\quad\;\;| \\ R_2C-CR_2 \end{array}$$

which could become stabilized either through rearrangement into isozonides or through polymerization to higher molecular forms. He arrived at this hypothesis because, firstly, both monomeric and polymeric ozonides can be obtained from the same substance by using different solvents, and, secondly, the monomeric ozonide once formed cannot be polymerized. On this account, it appeared necessary to assume that these are secondary products, and that, initially, a primary ozonide, a so-called molozonide, is formed, which can either polymerize or undergo rearrangement into the stable monomeric form, the so-called isozonide. The lability of the molozonide is a logical consequence of its four-atom ring structure. The frequent explosions encountered in the action of ozone on unsaturated organic compounds can be attributed to the decomposition of such an unstable product. Harries (67) states, for example, that, in the ozonization of amylene in a concentrated hexane solution, the liquid suddenly inflames, whereas the pure amylene ozonide can be heated to 60°C. without exploding. In the latter case, the molozonide is assumed to have been converted through rearrangement into the more stable five-atom ring isozonide. Staudinger represents these assumptions as follows:



This formulation is analogous to the formation of an unstable monomeric peroxide, a so-called moloxide (37), which can then either rearrange or polymerize.

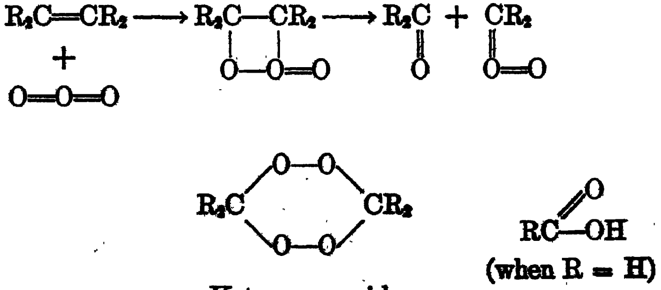


The less labile five-atom ring configuration of the isozonide favors its formation by rearrangement, and is the formula assigned to all stable monomeric ozonides, which include those of all aliphatic ethylenic derivatives, the monomeric form of cyclopentadiene, dicyclopentadiene, oleic acid and also the ozonide of rubber. The fact that the products of reduction are aldehydes and ketones or the corresponding alcohol, and the fact that glycol derivatives have never been obtained, are favorable indications of the validity of the isozonide formula.

In connection with the polymeric ozonides, it is interesting to note, in support of this hypothesis, that such products have always been observed where they would be expected: namely, where the rearrangement would be difficult, particularly where the double bond is in a ring. These cases include cyclopentene, cyclohexene, cycloheptene, dicyclopentadiene, dihydrodicyclopentadiene, and ozonides of aromatic compounds.

The effect of the solvent is also important. In acetic acid, where association of molecules does not readily take place because of its polar character, monomeric ozonides are almost invariably obtained. On the other hand, in carbon tetrachloride, which is non-polar and favors association, the polymeric form is the rule.

Staudinger visualizes a third reaction of a molozonide, to satisfy those cases where no stable ozonide can be isolated, in which an immediate breakdown of the molecule takes place, yielding a ketone and a ketone peroxide.

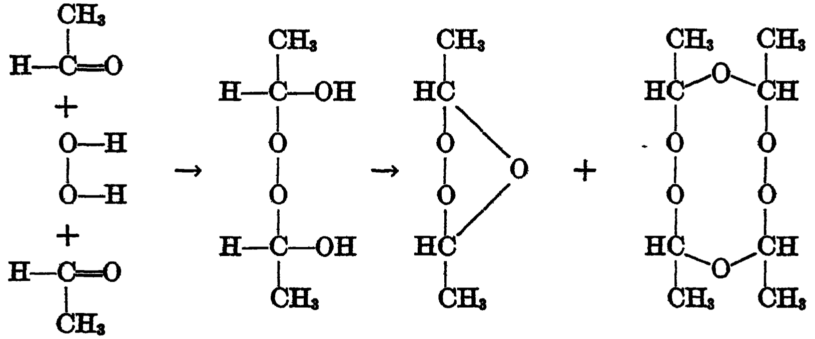


$$R_2C{=}CR_2 + O{=}O{=}O \longrightarrow \underset{O-O=O}{R_2C-CR_2} \longrightarrow \underset{O}{\overset{\|}{R_2C}} + \underset{O=O}{\overset{\|}{CR_2}}$$

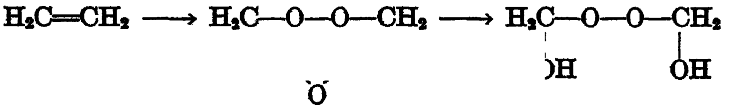
Ketone peroxide

Staudinger considered his theory an important new conception of the constitution of ozonides; it has been partially substantiated, though not completely proved. He considered its analogy to the action of oxygen to form peroxides a strong factor in its favor.

Since the publication of this paper (142), the constitution of the monomeric butylene isozonides has been partially proved synthetically. Rieche (127), in 1932, reported the synthesis of a substance which he stated to be identical with the ozonide obtained by ozonization of butylene. By the addition of 2 moles of acetaldehyde to a 3 per cent ethereal solution of hydrogen peroxide, a solution of dihydroxy ethyl peroxide was obtained, which yielded, on removal of the ether *in vacuo* and subsequent dehydration *in vacuo* in the cold, a small amount of the monomeric butylene isozonide together with a larger quantity of its dimer, as follows:



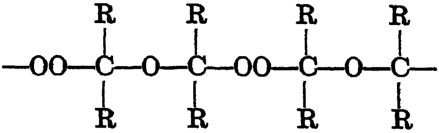
The isozonide theory also offers a simple interpretation of the formation of a peroxide by hydration of the ozonide of ethylene, reported by Briner and Schnorf (21).



$$H_2C{=}CH_2 \longrightarrow \underset{\displaystyle O}{H_2C{-}O{-}O{-}CH_2} \longrightarrow \underset{OH}{H_2C}{-}O{-}O{-}\underset{OH}{CH_2}$$

Other evidence in favor of Staudinger's formula was obtained by Rieche (126) from a consideration of the physical properties of ethylene and butylene ozonides. A comparison of the molecular refraction, the parachors, and the ultraviolet absorption spectra of these substances with those for monohydroxy dimethyl peroxide, dimethyl peroxide, and monohydroxy ethyl methyl peroxide, indicated the presence of a similar group in both types of compounds. As a result, Rieche concluded that two of the oxygen atoms in an ozonide form a peroxide linkage, and that the third oxygen forms an ether bridge.

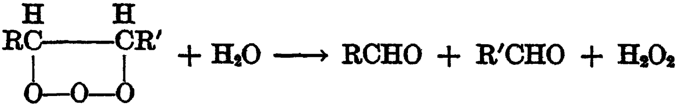
Rieche has suggested an alternate formula for polymeric ozonides to that proposed by Staudinger: namely,—



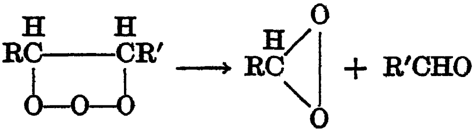
$$-OO-\underset{R}{\overset{R}{C}}-O-\underset{R}{\overset{R}{C}}-OO-\underset{R}{\overset{R}{C}}-O-\underset{R}{\overset{R}{C}}-$$

It is based on the alternation of ether and peroxide linkages, and consequently finds some support from the ultraviolet absorption spectra of these compounds.

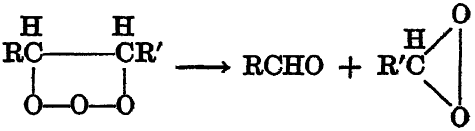
Harries presented his ozonide formula on the basis of investigations of the products of decomposition of ozonides, which he found to include acids, aldehydes (or ketones), and frequently peroxides. Harries conceived the following scheme of decomposition (54):



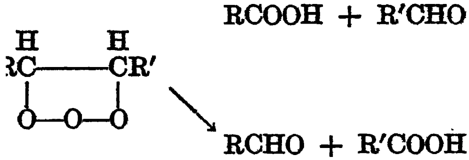
(1)



(2)



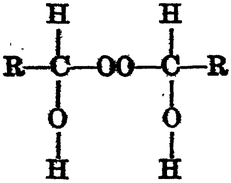
(3)



(4)

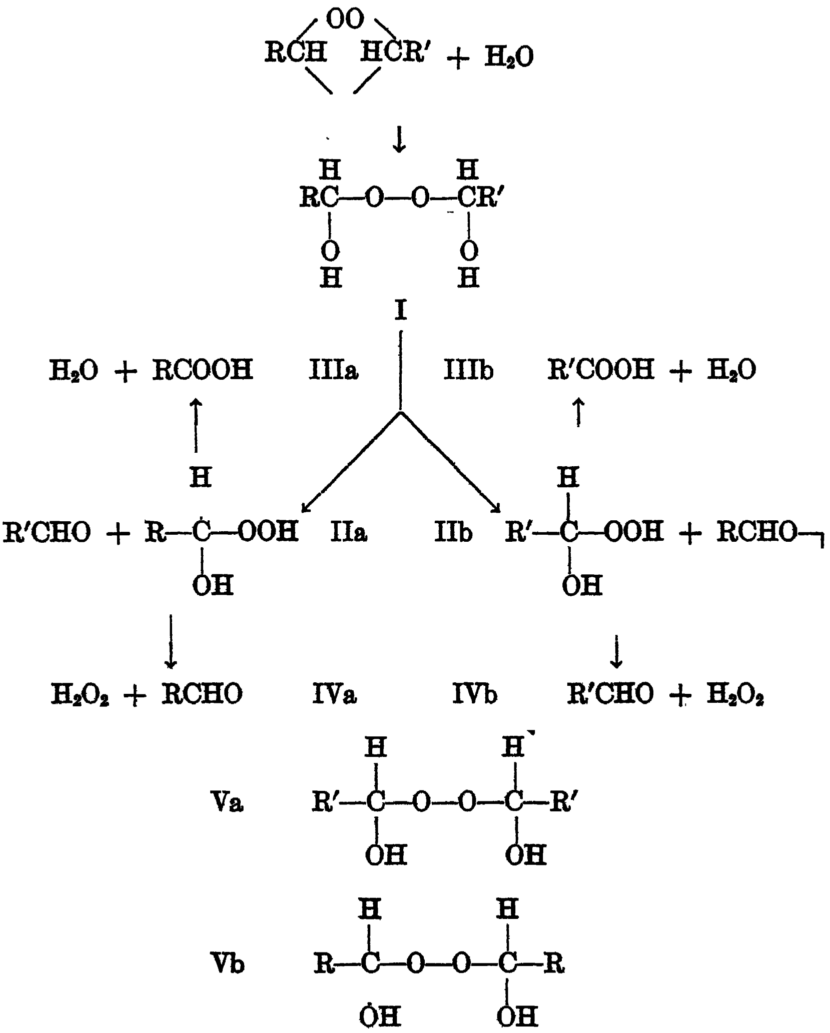
(5)

Rieche maintained this decomposition mechanism to be improbable for three reasons: (*1*) The indubitable rôle of water becomes thereby inconsiderable. (*2*) The peroxide bridges of the ozonide are broken. This contradicts his experience with alkyl peroxides. (*3*) The peroxides resulting from decomposition, which show stability, have a different constitution than Harries assumed. Molecular weight determinations indicate a double value, and the peroxides should be formulated thus:



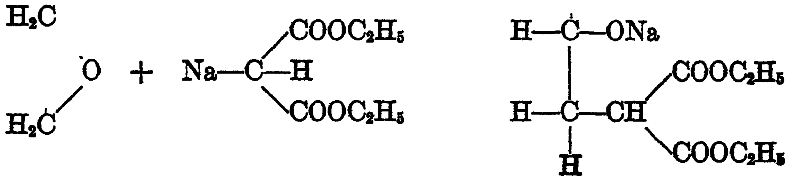
$$R-\underset{OH}{\overset{H}{C}}-OO-\underset{OH}{\overset{H}{C}}-R$$

Rieche (126), in 1931, developed a new scheme (see below) of decomposition, based on much experimental work, which apparently accounted for all the known facts.

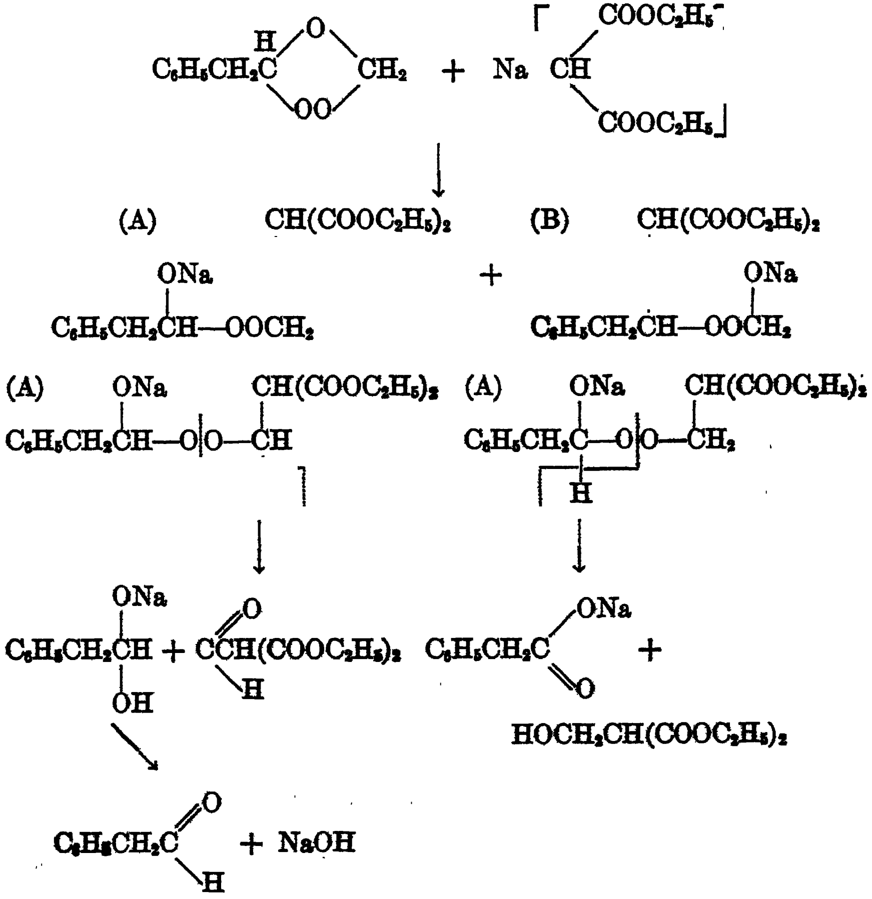


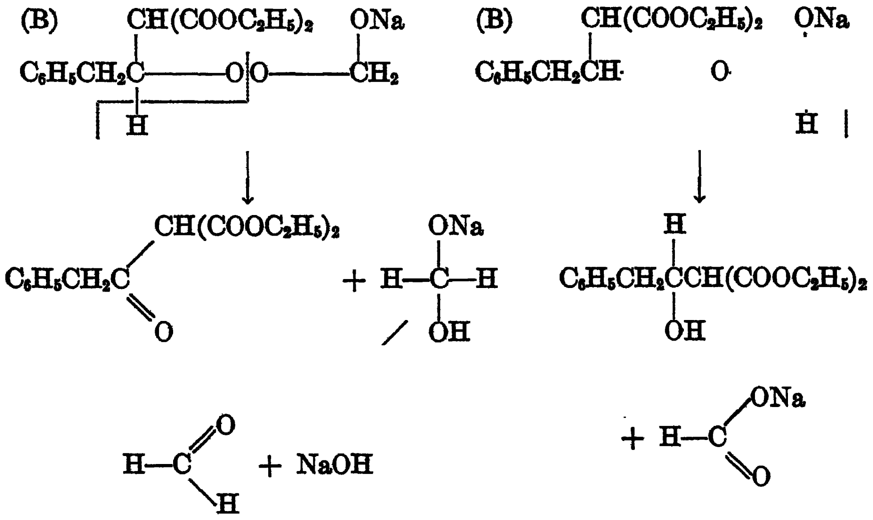
The sequence and probability of the various steps in the decomposition was supported by Rieche by analogy to similar processes occurring with alkyl peroxides.

An interesting substantiation of Rieche's ozonide formula and of his ozonide decomposition mechanism has been obtained recently by W. Lehmann (102). Allylbenzene ozonide was treated with sodium malonic ester, and the resulting product decomposed with water. This reaction was attempted because W. Traube and E. Lehmann (148) had reported that sodium malonic ester and ethylene oxide react vigorously in the following manner:

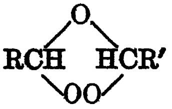


Since a like grouping is assumed to be present in ozonides, a similar reaction should occur. The reaction was assumed to follow the course outlined below.



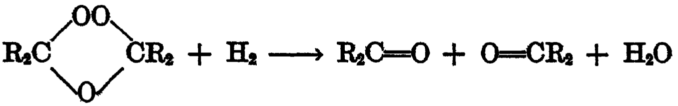


By the isolation of formic acid, phenylacetic acid, β-benzoylisosuccinic acid, an unsaturated lactone ester ($C_{13}H_{12}O_4$), the half-acetal of phenylacetaldehyde and ethyl alcohol, and a dihydroxytetracarboxylic acid ($C_8H_{10}O_{11}$), secondary products anticipated by the above mechanism, it was shown that the ozonide must have had the Staudinger structure,

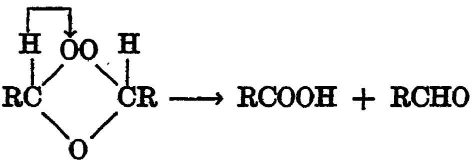


and, since these products could not have been obtained from the ozonide formula of Harries, the latter must be rejected.

F. G. Fischer (42), in 1932, described an improved method of decomposing ozonides by catalytic hydrogenation, whereby a marked improvement in the yield of aldehydes and ketones was obtained. On the basis of the Staudinger formula, the mechanism was assumed to be



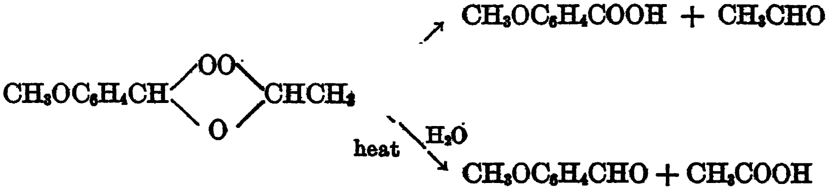
(6)



(7)

Equation 7, the so-called "acid rearrangement", was observed to take place as a secondary reaction to the hydrogenation. The yield of acid was found to vary proportionately with the temperature of hydrogenation.

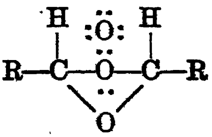
In 1938, Briner (18) tentatively suggested an alternate ozonide formula in order to account for certain properties of ozonides which had been observed in his laboratory. His experiments indicated that certain ozonides can decompose in two ways. For example, anethole ozonide yielded, in the absence of water, chiefly anisic acid and acetaldehyde, whereas hot water, with acceleration of the reaction, gave anisaldehyde and acetic acid.



It was also found, by treatment of the ozonide with potassium iodide, that an amount of active oxygen was present corresponding to that required for the addition of 1 mole of ozone per mole of anethole. It was concluded, therefore, that a characteristic property of the ozonide molecule is the retention of the peroxide activity possessed by the mole of ozone added. The Staudinger formula was found to account for the first observation with respect to the two methods of decomposition of the anethole ozonide, but it was held to be an inadequate representation of the peroxide character of the compound.

The contention was that the oxygen atom endowed with peroxide properties does not occupy a special position in the formula. The only oxygen atom which has a special position is known to function like the oxygen of an anhydride on the basis of the hydration of ozonides and dehydration of peroxides previously referred to. The peroxide oxygen atom is therefore one of the two others, and it is in connection with this formulation that a question has been raised. A similar problem exists in the case of the peroxides.

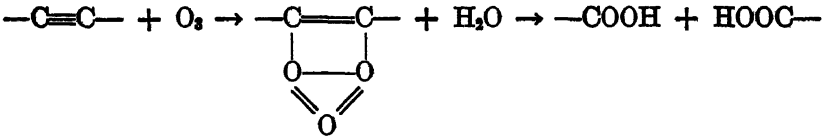
One method of separately identifying one of the atoms is to use a coordinately bound oxygen atom.



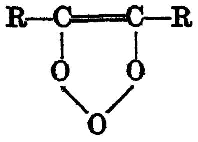
This type of formula has been suggested for hydrogen peroxide (111) and other peroxides (143) by many authors, but it has inspired much opposition because the expected products of decomposition have not been observed

(8, 157). For these reasons, Rieche placed the two oxygen atoms adjacent to each other without a bond, thereby admitting implicitly that the oxygen bridge —OO— determines the peroxide action. On the basis of recent work with Raman spectra (11), certain Russian authors have reconsidered a coördinately bound oxygen atom in peroxides. Without discussing it further, Briner has indicated the possibility of renewing the consideration of peroxide and ozonide formulas.

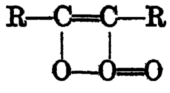
The theory of the ozonization of acetylenes has been developed to a lesser extent than for olefins. Harries (55, 56) was the first to attempt the addition of ozone to a triple bond. Practically quantitative yields of the acids anticipated from scission of the triple bond were obtained from the ozonization of stearolic acid and phenylpropiolic acid. Consequently, Harries formulated the reaction in an analogous manner to that for olefins, with the substitution of acids for aldehydes, or ketones, as the reaction products.



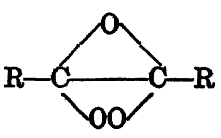
In 1929, Briner and Wunenberger (22) improved the work of Wohl and Braunig (162) by isolating glyoxal in 81 per cent yield from the ozonization of acetylene. This was an exception to the previously observed phenomena, in that it represented the only instance wherein the —C—C— bond had not been broken by the decomposition of an ozonide. More recently Hurd and Christ (83) have discussed the course of the ozonization of acetylenes. By analogy to the olefinic structures, three possible formulas were suggested. Formula I is a modification of Harries' structure, whereas formulas II and III correspond to Staudinger's molozonide and isozonide representations. All of the various formulas satisfactorily interpret the evidence of hydrolysis, giving rise to acids, *via* α-diketones (or glyoxals) and hydrogen peroxide. In the case of glyoxal formation from acetylene ozonide, the reactions would be:



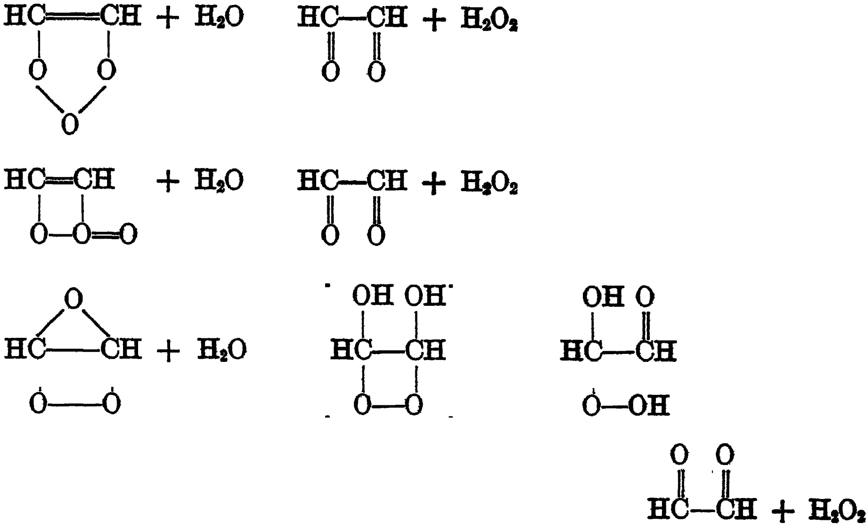
I



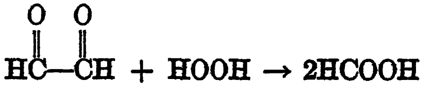
II



III



In all cases, the subsequent reaction is



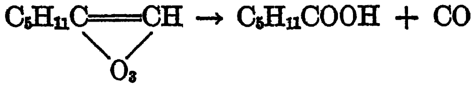
$$OHC{-}CHO + HOOH \rightarrow 2HCOOH$$

By analogy to the olefins, the authors favored structure II, in preference to I, for the initial addition product.

Shortly thereafter, Jacobs (84) reported the isolation of 1,2-diketones from the ozonization of diphenylacetylene and benzylphenylacetylene, evidence which offered strong support for the formation of such compounds as intermediates in the ozonization of acetylenic substances. The amorphous character of the unstable product of ozonization at low temperatures indicated that it was polymeric, whereas Hurd and Christ assumed the formation of only monomeric species. Another example of a similar nature has been reported currently for the ozonization of benzoylmesitylacetylene (45) to mesityl phenyl diketone. Although mesityl phenyl triketone would be expected as the primary product of the action of ozone, it is known (46) that the diketone is a decomposition product of the triketone.

$$C_9H_{11}C{\equiv}CCOC_6H_5 \rightarrow C_9H_{11}COCOCOC_6H_5 \rightarrow C_9H_{11}COCOC_6H_5$$

Another theoretical interpretation (118) of the decomposition of acetylene ozonides has been suggested recently, prompted by the observed decomposition of 1-heptyne ozonide into caproic acid and formic acid but with an abnormally low yield of the latter. This low yield could be accounted for by a spontaneous decomposition of the ozonide into caproic acid and carbon monoxide.



$$C_5H_{11}C\underset{O_3}{=\!=}CH \rightarrow C_5H_{11}COOH + CO$$

As a mechanism, the authors suggested that the unstable ozonide rapidly rearranges into the mixed anhydride of caproic and formic acids, $C_5H_{11}COOOCH$, which would decompose into caproic acid and carbon monoxide, as observed by Behal (10) for the mixed anhydride of acetic and formic acids. This suggestion of Paillard and Wieland appears to be substantiated by very little experimental evidence. The work of Jacobs and Fuson, in which 1,2-diketones were isolated, indicating that the original carbon-to-carbon bond was unbroken, presents facts of a definitely contradictory nature, of which Paillard and Wieland were not cognizant.

III. THE METHODS OF OZONIZATION

Although ozonolysis has been referred to frequently as the most suitable method for the location of an unsaturated carbon-to-carbon linkage, its application in many laboratories has been curtailed by the lack of a suitable ozonizer. In the papers of Smith (139) and Henne (75), a simple, efficient, inexpensive apparatus is described which has been designed to generate ozone of high concentration.

The vessel in which the ozonization takes place has apparently received less attention from experimenters than almost any other phase of the reaction. Its construction, however, materially affects the use of the method, and is a subject which deserves more consideration. The problem is chiefly one of contact between a gas and a liquid, and is met usually by merely inserting a gas inlet tube (78) in a test tube. Vollmann and coworkers (150) advocated the use of a tube with a fritted-glass bottom, a decided improvement over the usual method. An isolated instance of an interesting modification of the ozonization reaction vessel has been described in the application of a countercurrent flow of ozone and the solution to be ozonized through a tower packed with small glass rings (122).

It has been found necessary to vary the concentration of ozone in the ozonized oxygen bubbled through the solution to be ozonized, in accordance with the nature of the compound being tested. A high concentration, 14 or 15 per cent, facilitates addition of the reagent to aromatic compounds and substances with conjugated double bonds (78, 103), whereas a low concentration, 1 to 5 per cent, is essential for the isolation of certain aldehydes which are sensitive to oxidation. To reduce the concentration of ozone, the gas stream is passed through a solution of sodium hydroxide before entering the ozonization vessel. In the ozonization of ergosterol

(123), an abnormally high oxygen concentration was found in the ozonide isolated when 8 to 10 per cent ozone was used. By reducing it to about 2 per cent, the normal ozonide was obtained, which led to the elucidation of the side-chain structure. In almost every instance, excessive ozonization must be avoided, because of the oxidative effect of the ozonized oxygen on the reaction products. When complete absorption of ozone does not occur, this factor becomes one of the most difficult problems in the reaction.

A number of solvents have been found useful by various workers, and no very general rules can be given. Although substances which are attacked by ozone would seem to be inapplicable, this is not necessarily the case, for methyl alcohol (15), chloroform, and other liquids known to be sensitive to ozone have been used successfully. In special cases, as in the ozonization of maleic acid (15, 57), water also has been found to be suitable. Dry pure ethyl acetate was stated by F. G. Fischer (42) to be the best solvent for a number of alicyclic and straight-chain unsaturated compounds. Acetic acid (with and without the addition of acetic anhydride), hexane, petroleum ether, carbon tetrachloride, and methyl and ethyl chlorides have been used frequently and successfully.

The concentration of the solution may be varied widely, but for most olefins dilute solutions and low temperatures are preferable (42). For aromatic substances, in cases where the material is a liquid, no solvent is necessary, as exemplified by Harries' classical ozonization of benzene (73). However, the danger of explosion is here greatly magnified.

The effect of structure on the relative stability of the ozonides of different compounds has been noted in a few instances. The ozonolysis of aromatic compounds has frequently led to substances of an explosive nature (53). In a study of the ozonization of the dehydration products of the alcohols R_3COH, $R'R_2COH$, and $R'R''R'''COH$ containing normal alkyl groups from methyl to *n*-amyl, it has been reported recently (30) that, though most of the ozonides showed little explosibility, those of the highly branched and heavier olefins were the most unstable to light and heat.

IV. THE METHODS OF DECOMPOSITION

The significance of the ozonization method for the proof of structure and preparative purposes is diminished greatly because of the often unsatisfactory decomposition of the ozonide. Little exact work has been done on these methods.

In general, the ozonides of the higher aliphatic, simple, unsaturated hydrocarbons are very stable, like those of hydroaromatic substances. On the other hand, the ozonides of the doubly unsaturated, aliphatic hydrocarbons decompose readily. Aliphatic ozonides containing oxygen in other parts of the molecule react readily, in almost every case, with ice water. Similarly, decomposition of ozonides of benzal compounds and their oxygen derivatives takes place very quickly. Of the different ring systems, the ozonides of six- and seven-membered ring compounds are stable in comparison with those of five-membered ring compounds. Ozonides of compounds of very high molecular weight, like rubber, resinify when heated with water, owing to intramolecular oxidation.

Because of the explosibility of the ozonides of the keto chlorides of unsaturated ketones and aldehydes, Straus (146) developed a useful application of the decomposition with water. By drawing a stream of moist air through the ozonized solution, and thereafter adding water and heating, it was found possible to decompose gently these extremely unstable compounds, and to isolate products which could be used to prove the structures of the keto chlorides of benzalacetophenone, $C_6H_5CCl{=}CHCHClC_6H_5$, cinnamylideneacetophenone, $C_6H_5CCl{=}CHCH{=}CHCHClC_6H_5$, dibenzalacetone, $C_6H_5CH{=}CHCCl{=}CHCHClC_6H_5$, and cinnamal chloride, $C_6H_5CH{=}CHCHCl_2$.

Methods of oxidative cleavage of ozonides lead to acids as the products of ozonization, and have found relatively few applications. Düll (35) has made a comprehensive investigation of a number of different oxidants, including chromic acid, alkaline and acid potassium permanganate, alkaline hydrogen peroxide, Caro's acid, nitric acid, iodine in alkaline solution (160), and catalytic oxidation with manganous hydroxide, manganous acetate, and palladium as catalysts. Decomposition with alkaline permanganate or with hydrogen peroxide in alkaline solution proved to be the most useful methods.

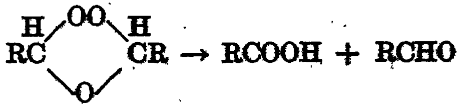
The important isolation of geronic acid and isogeronic acid from the ozonization of α-carotene in glacial acetic acid was accomplished by Karrer (91) by decomposition of the ozonide with water and a small amount of hydrogen peroxide.

Since, in many cases, it is essential to isolate certain aldehydes or ketones, instead of acids, as products of decomposition of ozonides, methods of reductive decomposition have been investigated extensively. Treatment of the ozonide with the reducing reagent without delay after the ozonization has been found essential for the avoidance of acid decomposition products in many cases. In Pummerer and Richtzenhain's (122) apparatus for countercurrent flow of ozone and the solution of the substance to be ozonized, the decomposition is accomplished without any delay, as the ozonized solution flows directly into the flask containing the reducing agent. Aluminum amalgam and water was found to be a good reducing agent for mesityl oxide ozonide, as well as a mixture of water, zinc dust, silver nitrate, hydroquinone, and dioxane. For the decomposition of the very stable ozonide of dihydrodicyclopentadiene, it was necessary to resort to zinc dust, glaical acetic acid, and heat. 3,6-endo-Methylenehexahydrohomophthalic dialdehyde was isolated in fair yield. Potassium ferrocyanide was found by Harries (58) to serve well for the preparation of particularly sensitive aldehydes and ketones, since the formation of tarry products was retarded.

Whitmore and coworkers (30, 152) have made a thorough study of various methods of decomposing ozonides, including the use of zinc and acetic acid (66, 114), of potassium ferrocyanide (58), of sodium bisulfite (21), of catalytic hydrogenation (40, 42), and of other new methods involving the action of acetic anhydride, propionic anhydride, liquid ammonia, and hydrazine hydrate solution. The olefins employed in this study of ozonolysis were obtained by dehydration of some twenty-two tertiary alcohols containing various combinations of normal alkyl groups, from methyl to amyl. The best method for decomposing the ozonides was by treatment with water and zinc in the presence of traces of silver and hydroquinone. The effectiveness of these catalysts was indicated by the following yields of carbonyl products isolated: acetaldehyde, 38 per cent; propionaldehyde, 18 per cent; butyraldehyde, 27 per cent; valeraldehyde, 38 per cent; diethyl ketone, 57 per cent; and di-*n*-amyl ketone, 63 per cent. Although this method proved to be most successful in the hands of Whitmore and coworkers, it has not had a wide acceptance. It involves several disadvantages: the isolation of a pure ozonide is often impossible, owing to the instability of the compound; the apparatus is complicated, and when destroyed by explosions, which can readily occur, is difficult to replace. As a result, the method of catalytic hydrogenation, discovered by F. G. Fischer (40), has received a more widespread acceptance, and appears to be the best method of reductive decomposition.

Düll (35) made a series of experiments to determine the utility of ozonolysis as a preparative method for aldehydes. The use of potassium ferrocyanide, sodium sulfite, sodium bisulfite, and catalytic hydrogenation was tested with oleic acid; the highest yield of aldehydes was obtained with the last method.

Certain precautions have been found to increase the yields of aldehydes and ketones (42): e.g., ozonization in dilute solutions and at low temperatures, careful avoidance of an excess ozonization, and hydrogenation at low temperatures. The hydrogenation usually proceeds very quickly and with much evolution of heat. The resultant secondary reaction, an "acid rearrangement" of the ozonide, increases with the temperature, and was found to be the main cause of low yields. The formation of acid becomes



negligible, however, if warming is prevented during the hydrogenation. By consideration of these precautions, yields of 50 to 90 per cent of the theoretically possible quantity of aldehydes or ketones were obtained. Some sensitive dialdehydes,—glutaraldehyde, adipaldehyde, and pimelaldehyde,—were isolated in 50 to 75 per cent yields. These results may be compared with a 5 per cent yield of glutaraldehyde from cyclopentene ozonide by water decomposition, according to Harries (71), and a 20 per cent yield of glutaraldehyde and adipaldehyde obtained from cyclopentene and cyclohexene ozonides, respectively, by reduction with titanous chloride, reported by R. Robinson (110).

The hydrogenation of highly polymerized ozonides,—for example, solid cyclohexene ozonide,—did not proceed at room temperature, but was accomplished by warming in an autoclave with hydrogen under pressure. Decomposition of the resulting aldehyde was retarded by the use of methanol or ethanol as the solvent, whereby unreactive acetals were formed. A 60 per cent yield of adipaldehyde was thus obtained.

It was found preferable, however, to ozonize in a solvent in which highly polymerized insoluble ozonides did not form. Ethyl acetate was found particularly useful; cyclohexene ozonide prepared in this solvent remained completely in solution. Ethyl acetate was not appreciably attacked by ozone, as long as olefin was still present in solution (41), and had the added advantage that hydrogenation could be accomplished in the same solvent. Halogenated solvents, such as ethyl chloride, chloroform, or carbon tetrachloride, had to be distilled before reduction. The hydrogenation flask was cooled with ice water during the shaking process; 0.5 g. of catalyst,—palladium on calcium carbonate (24), with 5 per cent palladium content,—was used for each reduction.

An interesting application of the catalytic hydrogenation method has been made by Pummerer (121). By hydrogenation of carotene ozonide in glacial acetic acid with a platinum–charcoal catalyst, glyoxal was isolated in 3 per cent yield, giving additional evidence of a conjugated double bond structure. Another important characterization of a natural product was accomplished in the location of the double bond in the side chain of ergosterol (123) by catalytic hydrogenation of the ozonide of ergosterol acetate. The hydrogenation was carried out in a 1:1 ether–glacial acetic acid mixture as solvent with platinic oxide as the catalyst. The isolation of methylisopropylacetaldehyde was an unexpected result on the basis of the previous work on ergosterol, and rectified the former conception of the side chain.

V. RATES OF OZONIZATION

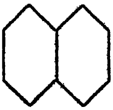
The relative rates of ozonization of different compounds have been little studied. In 1910, Harries (54) observed that compounds containing two conjugated double bonds add the first mole of ozone more rapidly than the second. Brus and Peyresblanques (23), in 1930, presented curves for the ozonization of pinene, limonene, and oleic acid, in which the unabsorbed ozone was plotted against liters of oxygen used. The results indicated that, for an aliphatic double bond, ozone was absorbed quantitatively until the double bond was saturated. Thereafter, the amount of unabsorbed ozone increased very rapidly for a time, and finally gradually approached the original ozone concentration. These observations were interpreted as indicating that perozonides were formed by over-ozonization, after the completion of the formation of the normal ozonide. Harries (59) had postulated the simultaneous formation of ozonides and perozonides, owing to the presence of oxozone in the ozonized oxygen. Brus and Peyresblanques doubted the hypothesis of Harries, and agreed with Kailan (87) and Riesenfeld (128) that the existence of oxozone is improbable. In a second paper (23), also in 1930, curves were given for the ozonization of styrene, phenylcyclohexene, benzene, and heptyne. With the concentrations of ozone used, 9 to 10 per cent, benzene added ozone extremely slowly and heptyne moderately so, while the other compounds added 1 mole of ozone very rapidly.

In 1936, Noller (115) and coworkers extended the procedure of Brus and Peyresblanques to the rates of ozonization of a number of other compounds. Curves were shown in which an "adjusted" per cent of unabsorbed ozone was plotted against the equivalents of ozone entering the solution. From the ozonization curves for some twenty-one compounds of varied structure, it was possible to draw certain interesting conclusions. Whereas a double bond, unaffected by the presence of other groups, was found to add ozone extremely rapidly, the rate was markedly decreased when the double bond was conjugated with carbonyl groups. Three or more phenyl groups or two chlorine atoms attached to the doubly bound carbon atoms also decreased the rate of addition. Where two or three double bonds were conjugated with each other, one bond added ozone rapidly while the others added it only slowly. In the case of *cis–trans* isomers, where the rate of addition was decreased by other groups, the *trans*-isomer was found to add ozone more rapidly than the *cis*-form. The latter fact has recently been corroborated by Briner (15).

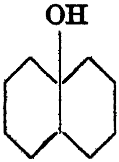
VI. OZONE AS AN OXIDANT

The oxidation of saturated hydrocarbons and other saturated compounds with ozone has received the attention of but few investigators. This may be ascribed to the importance of the ozone reaction with unsaturated compounds, and to the complexity of the reaction mixtures obtained in the oxidation reaction. Harries (53) observed that aliphatic hydrocarbons such as hexane, petroleum ether, and ligroin were slowly attacked by ozone. Mixtures of different compounds were found, including ozonides, peroxides, and fatty acids. Hexane yielded valeraldehyde and adipic acid in addition to other unidentified substances. Recently, a quantitative study of the oxygen consumption of various aliphatic hydrocarbons in the presence of both oxygen and ozone in the gaseous state has indicated (14) that a chain mechanism best explains the results. The compounds studied included all the lower members of the homologous series through normal octane, and two isoöctanes. In every case, a catalytic effect of ozone was found. For the straight-chain hydrocarbons, the catalytic effect occurred at lower temperatures than for the higher members. The branched-chain hydrocarbons exhibited a marked resistance to the oxidative effect of ozone. As the dilution of ozone increased, its catalytic action also increased, a fact consistent with a chain mechanism.

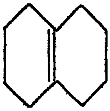
In an extended, but qualitative, investigation of the products of ozonization of technical decalin, Koetschau (95) identified α-decahydronaphthol amongst other substances which were considered to include peroxides and acids. Currently, Adkins (36) has investigated the problem further and, in connection with other work, has reported some interesting results for the action of ozone on cyclohexane, decalin, and certain hydrophenanthrenes. A variety of compounds were obtained, including saturated alcohols, ketones, acids, and unsaturated ketones and hydrocarbons. The yields, in several cases, were from 20 to 35 per cent of the theoretical. Among the saturated compounds, cyclohexane was the most resistant toward ozone, the products identified being cyclohexanone, formic acid, and adipic acid. *cis*-Decalin (IV) gave *cis*-decahydro-9-naphthol (V) and $\Delta^{9,10}$-octahydronaphthalene (VI) in good yields, and small amounts of *cis*-α-decalone (VII). A large quantity of a mixture of unidentified acids was also obtained.



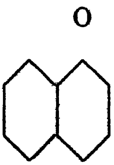
IV
cis-Decalin



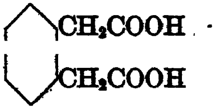
V
cis-Decahydro-9-naphthol



VI
$\Delta^{9,10}$-Octahydronaphthalene



VII
cis-α-Decalone



VIII
trans-1,2-Cyclohexanediacetic acid

trans-Decalin gave *trans*-decahydro-9-naphthol (V) and *trans*-α-decalone (VII) in 28 per cent yield, but unless special precautions were taken the chief product was the octalin (VI) in 21 per cent yield. A mixture of acids similar in amount to that from the *cis*-isomer was obtained. Among these was identified *trans*-1,2-cyclohexanediacetic acid (VIII). Similar results were reported for the ozonization of various hydrophenanthrenes.

The authors considered the course of the oxidation of the saturated hydrocarbons to have involved primarily a reaction of ozone at the tertiary carbon atoms, forming an hydroxyl group. Oxidation subsequently took place at secondary carbon atoms to give hydroxyketones. The dehydration of these alcohols gave unsaturated hydrocarbons or unsaturated ketones. Further oxidation gave acids.

The reactivity of ethers toward oxygen and ozone forms a striking characteristic of these unreactive compounds. For instance, ozone strongly oxidizes ethyl ether. This was one of the earliest observations (135) of the action of ozone on organic compounds. Among the products of oxidation, von Babo (5), later identified hydrogen peroxide, acetaldehyde, and acetic acid. Berthelot (12), by distillation of ozonized ethyl ether, obtained "ethyl peroxide", an explosive syrupy liquid, but was unable to prove its identity. It has since been shown by Harries (52) that this product was not homogeneous, but its explosibility deterred further investigation.

In two papers, published in 1929 and 1931, F. G. Fischer (41, 43) and coworkers reported the isolation and identification of the principal products resulting from the reaction of ozone with ethers, alcohols, and aldehydes, and were able to present a theoretical explanation of their formation. The oxidation of isoamyl ether was first carefully studied, and it was shown later that other ethers react similarly, including methyl ether, ethyl ether, butyl ether, isoamyl ethyl ether, and benzyl ether.

The first reaction was assumed to be the oxidation of the ether to an aldehyde and hydrogen peroxide, which would then interact to form a dihydroxy alkyl peroxide (156).

$$RCH_2OCH_2R + O_3 \rightarrow 2RCHO + H_2O_2$$

$$2RCHO + H_2O_2 \rightleftarrows RCH(OH)OOCH(OH)R$$

A further reaction was the formation of an ester and hydrogen peroxide. In the case of isoamyl ether, the isoamyl ester of isovaleric acid was isolated in 70 to 80 per cent yield.

$$RCH_2OCH_2R + O_3 \rightarrow RCOOCH_2R + H_2O_2$$

Fractionation of the products from the distillation of the butyl and isoamyl ether ozonizations gave fractions identified as the formic acid ester of the corresponding alcohols.

$$RCH_2OCH_2R + O_3 \rightarrow RCH_2OCHO$$

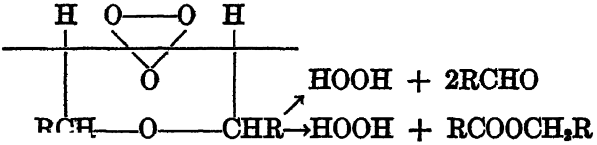
Methyl alcohol, ethyl alcohol, and isoamyl alcohol were ozonized also. The primary reaction was the formation of acids,

$$RCH_2OH + O_3 \rightarrow RCOOH + H_2O_2$$

accompanying which were found aldehydes to the extent of about one-fifth to one-third of the quantity of acid.

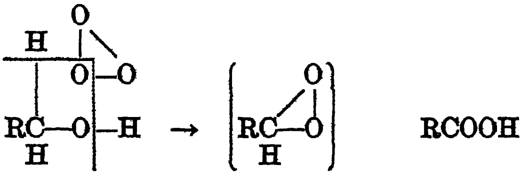
$$RCH_2OH + O_3 \rightarrow RCHO + H_2O + O_2$$

As an explanation of these reactions, Fischer has assumed the formation of an addition product as an intermediate, which would be very unstable and decompose rapidly. For the ethers, this would be



In this intermediate, the bridge oxygen becomes quadrivalent. This mechanism is analogous to certain peroxide rearrangements observed by von Baeyer (6), Harries (60), and others.

The formation of acids from primary alcohols may be written in a similar manner:



Fischer found that aldehydes formed mostly acids and per acids when subjected to the action of ozonized oxygen. Per acids were isolated and characterized from isobutyraldehyde, isovaleraldehyde, heptaldehyde, and benzaldehyde.

$$2RCHO + O_3 \rightarrow RCOOH + RCOO \cdot OH$$

To explain a lower yield of per acids than would be expected from the above equation, he assumed a second reaction to be

$$3RCHO + O_3 \rightarrow 3RCOOH$$

These reactions explained satisfactorily the reaction of the pure aldehydes with ozone, and accounted quantitatively for the ozone consumed. In solution, however, the amount of acids and per acids formed was larger than could be accounted for by the ozone consumption, indicating that oxygen had also taken part in the reaction. This was clarified by the assumption that the aldehyde added 1 mole of ozone to form a primary addition product, which then reacted with another mole of aldehyde to give per acids and acids; with 2 other moles of aldehydes to yield acids; or with oxygen to form per acids and ozone.

$$[\mathrm{RCHO{:}O_3}] \left\{ \begin{array}{l} \xrightarrow{\qquad\mathrm{RCHO}\qquad} \mathrm{RCOOOH} + \mathrm{RCOOH} \\ \xrightarrow{\qquad\mathrm{2RCHO}\qquad} \mathrm{3RCOOH} \\ \xrightarrow{\qquad\mathrm{O_2}\qquad} \mathrm{RCOOOH} + \mathrm{O_3} \end{array} \right.$$

The oxidation of ketones by ozone has not been as carefully investigated, but peroxide formation has been noted. The carbonyl group of aldehydes and ketones yields a peroxide relatively easily, whereas that of acids reacts with ozone only in the case of long-chain acids containing one or more double bonds.

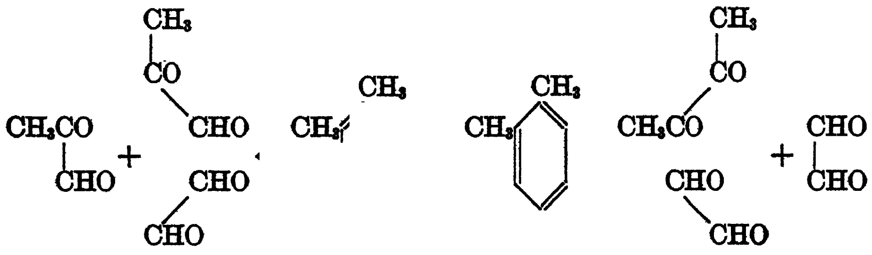
Amines are, in general, not attacked by ozone, nor are amino acids and acid amides (69). Aromatic amines, on the other hand, undergo deep-seated decomposition in some unknown manner. Harries has also oxidized dulcitol (69) and mannitol (69) by ozone and has isolated galactose, glucose, and fructose.

A knowledge of the oxidizing action of ozone is of importance in its reaction with a double bond, as an avoidance of this effect may account to a large extent for a reasonable yield of the desired products.

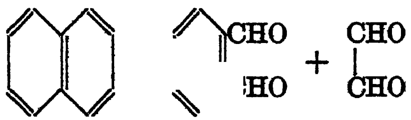
VII. THE OZONIZATION OF AROMATIC COMPOUNDS

The quantitative investigation of the ozonization of aromatic hydrocarbons was one of Harries' (52, 73) most noteworthy contributions. Houzeau (79), in 1873, and Renard (125), in 1895, had previously studied the ozonization of benzene. After overcoming many difficulties due to the explosibility of the substance, Harries was able to analyze quantitatively the reaction product of ozone and benzene. It proved to be a triozonide, as had been anticipated from the structure of benzene postulated by Kekulé. In addition, 2 moles of glyoxal were isolated per mole of ozonide on decomposition with water, a further corroboration of the Kekulé structure. Working with the pure substances, increasing difficulties were encountered in the ozonization of toluene and xylene. These ozonides could be formed only at very low temperatures, and were so explosive that it was found impossible to continue the experiments. On the other hand, it was possible to isolate the ozonide of mesitylene in a moist condition, and, on decomposition with water, to isolate methylglyoxal as the disemicarbazone. Since this was the only product that could be identified, it offered another confirmation of the Kekulé structure.

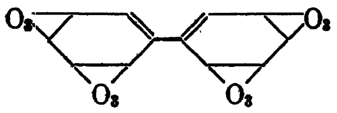
In 1932, Levine and Cole (103) demonstrated the existence of isomeric ortho-disubstitution products of benzene, by the ozonization of *o*-xylene in solution. Three products were identified after decomposition of the ozonide: namely, glyoxal, methylglyoxal, and diacetyl. Since neither form of xylene could have yielded all three oxidation products, the hydrocarbon must have consisted of an equilibrium mixture of the two Kekulé forms.



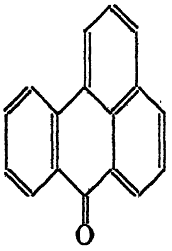
Polynuclear aromatic compounds add less ozone than the number of double bonds in the molecule should require. Naphthalene (52) was found to add only 2 moles to form a diozonide, from which *o*-phthalaldehyde and glyoxal were obtained by decomposition.



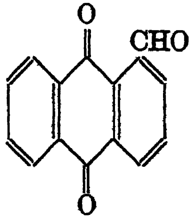
Phenanthrene behaved similarly; an analysis of the ozonization product proved the formation of a diozonide, but no products of decomposition could be identified. The insolubility of anthracene prevented its ozonization by Harries' methods, but it was possible to establish the formation of a diphenyl tetraozonide by analysis.



Recently, modern methods have overcome the obstacles encountered by Harries in the ozonization of anthracene. Vollman (150) and coworkers have reported several interesting ozonizations of polynuclear aromatic hydrocarbons. On the basis of results obtained with 1,9-benzanthrone and fluoranthene, it was possible to achieve an ozonization of pyrene suspended in glacial acetic acid. From 1,9-benzanthrone (IX) had been obtained the difficultly accessible anthraquinone-1-aldehyde (X) in 20 per cent yield,

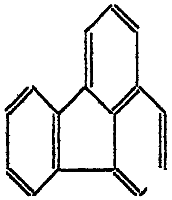


IX
1,9-Benzanthrone

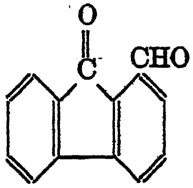


X
Anthraquinone-1-aldehyde

together with a large amount of anthraquinone-1-carboxylic acid; and fluoranthene (XI) had been ozonized in about 30 per cent yield to a mixture of fluorenone-1-aldehyde (XII) and fluorenone-1-carboxylic acid.

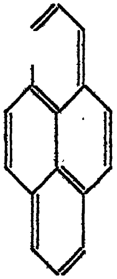


XI
Fluoranthene

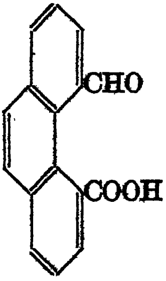


XII
Fluorenone-1-aldehyde

When pyrene (XIII) was treated with 0.5 per cent ozone and subsequently decomposed with water and sodium hydroxide, an excellent yield of 4-phenanthrenealdehyde-5-carboxylic acid (XIV) was obtained.



XIII
Pyrene



XIV
4-Phenanthrenealdehyde-5-carboxylic acid

The ozonides of the hydroaromatic compounds are different from those of either aliphatic or aromatic substances in their very unusual stability. It is difficult, and sometimes impossible, to decompose these ozonides with water.

An interesting study of the rate of absorption of ozone by aromatic compounds was made by Brus and Peyresblanques (23). The curves for benzene indicated a different phenomenon than that observed for compounds with an aliphatic double bond. In the latter case, no unabsorbed ozone was found until the double bond was saturated. Thereafter, this quantity increased rapidly, finally approaching the original ozone concentration. For benzene and naphthalene complete absorption was never observed, even with low concentrations of ozone and a large excess of the aromatic hydrocarbon.

VIII. OZONIZATION AS A SYNTHETIC METHOD

The earliest descriptions of the use of ozonization as a preparative method were made by Otto (117) and Trillat (149), who reported the commercial production of vanillin from isoeugenol and of piperonal from isosafrole. An improved method of decomposition of the ozonide was developed by Harries (66) in 1915, whereby a 70 per cent yield of vanillin was obtained. By the further application of the new method of decomposition, using zinc dust and acetic acid, several phenolic aldehydes (65) were prepared which had been hitherto unknown, including homovanillinaldehyde, methylhomovanillin, homopiperonal, and homoanisaldehyde. More recently Briner (19) has made an extensive investigation of optimum conditions of the reaction and has found, in the case of vanillin, that the best yields were obtained using a low temperature and a relatively high concentration of ozone.

Noller and Adams (114), in 1926, reported an investigation of the ozone reaction for the specific purpose of its utilization as a method of preparation. The aldehyde esters methyl η-aldehydoöctanoate (XV), methyl θ-aldehydononanoate (XVI), and methyl λ-aldehydododecanoate (XVII) were synthesized from methyl oleate, methyl undecylenate, and methyl erucate by ozonization. These substances should offer valuable starting materials, especially for the synthesis of acids of high molecular weight.

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH_3 \rightarrow CH_3(CH_2)_7CHO$$

$$+ \underset{\text{XV}}{CHO(CH_2)_7COOCH_3}$$

$$CH_2{=}CH(CH_2)_8COOCH_3 \rightarrow HCHO + \underset{\text{XVI}}{CHO(CH_2)_8COOCH_3}$$

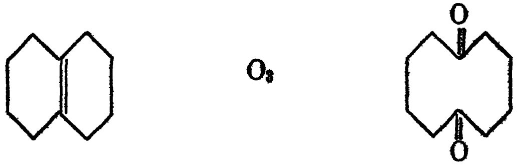
$$\mathrm{CH_3(CH_2)_7CH{=}CH(CH_2)_{11}COOCH_3 \rightarrow CH_3(CH_2)_7CHO} \\ \mathrm{+\ CHO(CH_2)_{11}COOCH_3} \\ \mathrm{XVII}$$

No difficulty was encountered in the isolation of over 55 per cent of the calculated amount of aldehyde ester boiling over a range of 5°C. In addition, pelargonaldehyde in yields of 60 to 70 per cent was obtained from methyl oleate and methyl erucate. The use of the aldehyde esters in synthesizing hydroxy acids and unsubstituted acids was illustrated by the conversion of methyl η-aldehydoöctanoate by means of butylmagnesium bromide into methyl θ-hydroxytridecanoate and, finally, conversion of this latter compound through the bromide and olefinic acid to tridecanoic acid.

The significance of ozonization for preparative purposes has been diminished frequently because of inadequate methods of decomposition. Acids and other undesirable secondary products are isolated instead of the anticipated aldehydes. F. G. Fischer and coworkers (42) have obviated these discouraging results to a large extent by the application of the method of catalytic hydrogenation to the ozonide decomposition. The sensitive dialdehydes glutaraldehyde, adipaldehyde, and pimelaldehyde were obtained in 50 to 75 per cent yield by ozonizing cyclopentene, cyclohexene, and cycloheptene, respectively.

Within the past few years several unusual instances of ozonolysis have been reported, which have interesting preparative applications. In particular, the formation of aldehydes in reasonable amounts by the ozonization of polynuclear aromatic hydrocarbons like 1,9-benzanthrene, fluoranthene, and pyrene, as previously described, should open new synthetic possibilities in this important field.

Of equal interest has been the use of ozone for the preparation of such an unusual compound as 1,6-cyclodecanedione (XIX) by W. Hückel (80). The latter was obtained from $\Delta^{9,10}$-octalin (XVIII) by ozonization. The diketone has been the starting point for significant syntheses in three directions.

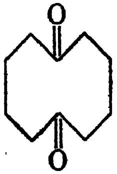


XVIII
$\Delta^{9,10}$-Octalin

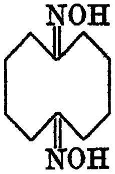
XIX
1,6-Cyclodecanedione

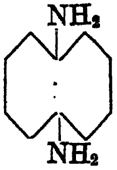
By reduction of the dioxime of XIX, exhaustive methylation, and catalytic hydrogenation, W. Hückel (81) has synthesized cyclodecane

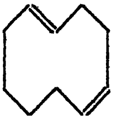
(XX), a compound which it has not been possible to prepare directly by the usual methods of closing an open chain or widening a ring with fewer carbon atoms (131).

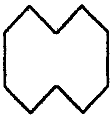


XIX
1,6-Cyclodecanedione



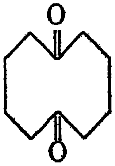




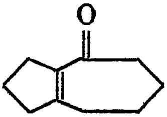


XX
Cyclodecane

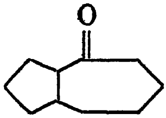
The diketone (XIX), when treated with either acids or alkalies, formed cyclopentenocycloheptanone (82) (XXI) by an inner-molecular aldol condensation followed by dehydration. This α,β-unsaturated ketone, on catalytic hydrogenation, gave a mixture of *cis-* and *trans*-cyclopentanocycloheptanones (XXII), interesting compounds from the point of view of the stereochemistry of bicyclic ring systems.



XIX
1,6-Cyclodecanedione

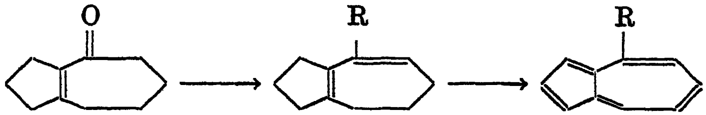


XXI
Cyclopenteno-
cycloheptanone



XXII
Cyclopentano-
cycloheptanone

In a third, and equally important, application, cyclopentenocycloheptanone (XXI) has been used as the starting material for the only synthesis of an azulene thus far described (147). By treatment of the ketone XXI with either methyl-, ethyl-, or phenyl-magnesium halide there was obtained a hydrocarbon with two double bonds (XXIII), which was dehydrogenated with sulfur, or catalytically with nickel, to yield the desired azulene (XXIV).

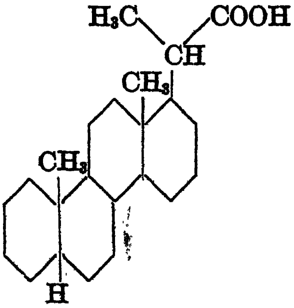


XXI
Cyclopenteno-
cycloheptanone

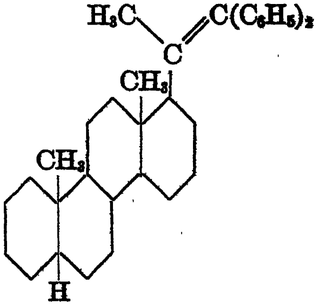
XXIII

XXIV

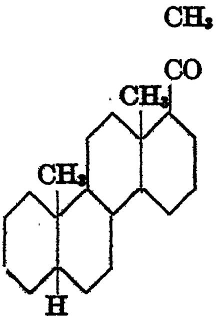
In the important and related fields of sex hormones and adrenal cortex hormones, the use of ozone as a preparative method has been applied in several instances. In 1931, Butenandt proved the structure of pregnanediol (25),—the interesting but oestrogenically inactive substance isolated from human pregnancy urine by Marrian (106),—by relating pregnane (XXVIII), the corresponding saturated hydrocarbon, to bisnorcholanic acid (XXV) in three steps. These involved a Wieland–Barbier degradation of the latter acid (XXV), ozonization of the resulting unsaturated hydrocarbon (XXVI) to yield the saturated ketone (XXVII), and finally reduction of the ketone by the Clemmensen method to give 17-ethyletiocholane (XXVIII), identical with pregnane.



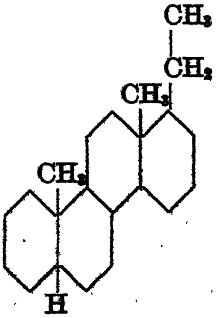
XXV
Bisnorcholanic acid



XXVI

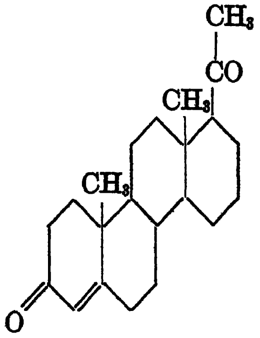


XXVII

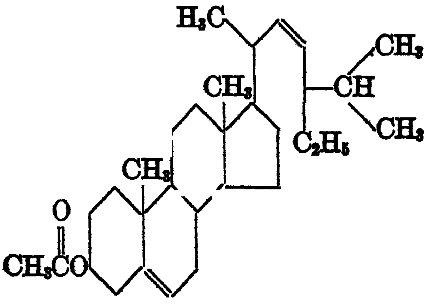


XXVIII
Pregnane

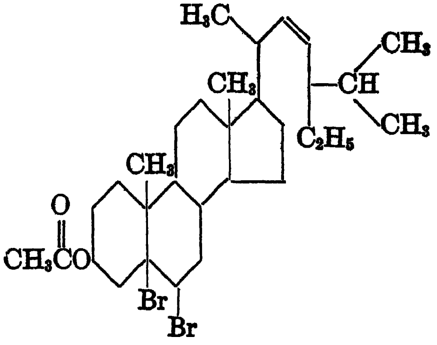
The isolation of acetoxybisnorcholenic acid from the ozonization of stigmasterol by Fernholz in 1933 (38) proved of value in the preparation of progesterone (XXIX), the corpus luteum hormone discovered by Corner and Allen in 1928 (31). The latter compound was prepared synthetically from stigmasterol at practically the same time by both Butenandt (26, 27, 28) and Fernholz (39), independently. The work of Fernholz involving the ozonization of stigmasteryl acetate dibromide also gave the first proof of the long-suspected relationship of stigmasterol to cholesterol, and completely established the carbon framework of the sterol. In the preparation of acetoxybisnorcholenic acid (XXXII), stigmasteryl acetate (XXX) was converted into the 5,6-dibromide (XXXI) by using just 1 mole of bromine. Ozone oxidation followed by dehalogenation with zinc, accompanied by simultaneous decomposition of the ozonide, gave the desired unsaturated acid (XXXII).



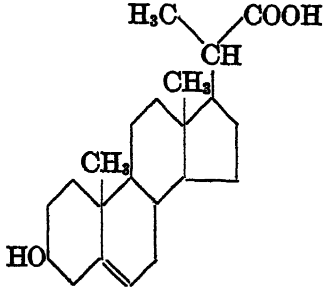
XXIX
Progesterone



XXX
Stigmasteryl acetate

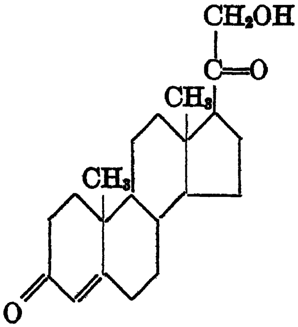


XXXI



XXXII
Acetoxybisnorcholenic acid

Later, in 1937, acetoxybisnorcholenic acid again proved useful in the synthetic preparation of desoxycorticosterone (XXXIII) by Reichstein (144). This compound has proved to be one of the most potent androgenic hormones isolated from the adrenal cortex.



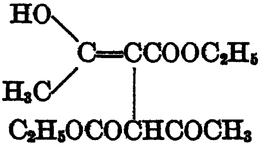
XXXIII
Desoxycorticosterone

IX. THE PROOF OF STRUCTURE BY OZONIZATION

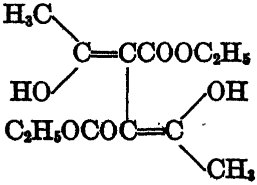
The most important application of ozone in organic chemistry is in the solution of structural problems by cleavage of unsaturated compounds, since the identification of the decomposition products presents the possibility of determining the position of the double bond. In most other reactions, only an addition to the double bond occurs, and its position cannot be inferred from the addition products.

An unusual application of the reaction has been its assistance in the determination of the constitution of enols, by ozonization of the enolic form of an enolizable substance (132). Few chemical methods were available for this determination at low temperatures without displacing the equilibrium. The formation and decomposition of the ozonide was carried out at low temperatures, under conditions which excluded rearrangement. β-Dibenzoylacetylmethane, for instance, does not add ozone, whereas its enolic tautomer readily forms an ozonide. Scheiber and Herold applied the method to numerous enolic compounds, including acetoacetic ester, ethyl oxalate, acetylacetone, benzoylacetone, and others. Abderhalden and Schwab (1) later applied the method to dihydroxypiperazines, dipeptides, and similar compounds.

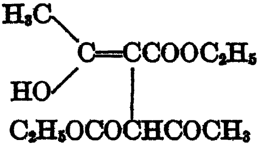
Kaufmann and Wolff (93, 94) combined ozonization with K. H. Meyer's bromine titration and ferric chloride colorimetric methods and were able to determine the three enolic forms of ethyl diacetylsuccinate. Bromine titration established the amount of the α_1,β-ester (XXXIV) present, a ferric chloride colorimetric titration the sum of the α-ester (XXXV) and the α_2,β-ester (XXXVI), and ozonization the total enolic content. The combination of the three determinations made possible a quantitative estimation of the relative amounts of the three enols.



XXXIV

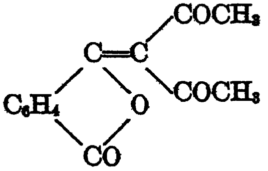


XXXV

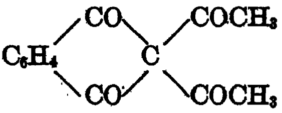


XXXVI

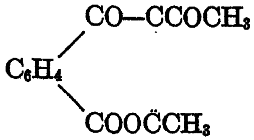
The problem of which structural isomer best represented the constitution of phthalylmalonic ester and similar compounds was solved by Scheiber and Hopfer (133) by the use of ozone. In the case of phthalylacetylacetone, structure XXXIX was shown to be correct, rather than XXXVII or XXXVIII, by the isolation of phthalic acid, methylglyoxal, and acetic acid as products from the decomposition of the ozonide.



XXXVII

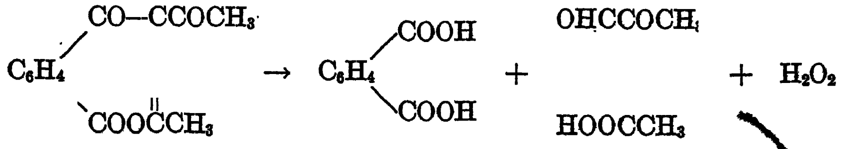


XXXVIII



XXXIX

Phthalylacetylacetone



An interesting use of ozone was in the clarification of the constitution of the keto chlorides by Straus (146) in 1912. By the application of this reagent it was possible to prove the structure of a whole series of these compounds. Cinnamyl chloride, one of the simplest examples, reacted with ozone and yielded benzaldehyde, benzoic acid, dichloroacetaldehyde, and dichloroacetic acid, after decomposition with water. As a result its constitution was proved to be $C_6H_5CH{=}CHCHCl_2$.

A more recent example of ozonolysis has been the proof of the structure of the two isomeric diisobutylenes discovered by Butlerow. McCubbin and Adkins (107) established definitely the presence of the two isomeric octylenes, 2,4,4-trimethyl-1-pentene (XL) and 2,4,4-trimethyl-2-pentene (XLI), by the isolation of methylneopentyl ketone, $(CH_3)_3CCH_2COOCH_3$, and trimethylacetaldehyde.

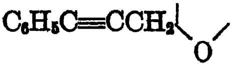
$$\underset{\text{XL}}{(CH_3)_3CCH_2C(CH_3){=}CH_2} \qquad \underset{\text{XLI}}{(CH_3)_3CCH{=}C(CH_3)_2}$$

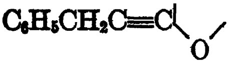
Their experiments indicated XL and XLI to be present in a ratio of approximately 4:1. Whitmore and Church (152) separated the low-boiling isomer from the higher boiling isomer by fractional distillation, and identified the low-boiling isomer with XL and the high-boiling component with XLI by the separate ozonization of each.

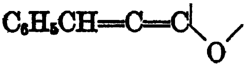
Ozonolysis as an indirect method of analysis has been exemplified in a series of papers published by Whitmore (30, 153, 154) in 1933 and 1934, dealing with the ozonization of purely aliphatic olefins. A variety of tertiary alcohols composed of different combinations of alkyl groups from methyl to *n*-amyl, and also 2,2-dimethyl-1-hexanol, containing a neo carbon atom, were converted into the chlorides, and hydrogen chloride was removed. The resultant olefins were then ozonized. The results were markedly successful, in that the decomposition products were isolated in good yields and served to indicate unequivocally the direction of the dehydration.

In the aromatic series, the importance of the structural proof offered by the use of ozone has been out of proportion to the few experiments reported. Harries' (73) ozonization of benzene and mesitylene offered proof for the Kekulé structure with three alternating double bonds, and Levine's (103) results with *o*-xylene strengthened the early evidence. In the case of the polynuclear aromatic compounds, the isolation of phthalaldehyde from the ozonide of naphthalene (52) located the position of two double bonds, and Vollman's (150) recent experiments with pyrene have established the position of one double bond of this high-molecular-weight hydrocarbon and confirmed the bond structure previously assigned to it.

The use of ozone for the elucidation of acetylenic structure has been even less extensive than its application to aromatic compounds, and the available examples are of recent date. By the isolation of phenylacetic acid as a product of the ozonolysis of Carlina-oxide (an oil obtained from the roots of *Carlina acaulis*), Gilman (48) was able to rule out formulas XLII and XLIV, leaving XLIII, benzyl-2-furylacetylene, as the structure of the compound.


XLII


XLIII

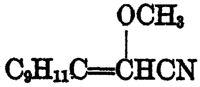

XLIV

Lai (100) has synthesized a series of β- and γ-diacetylenic compounds, and by ozonization has proved their structure. In the case of the β-diacetylenic compounds, diheptynylmethane was ozonized and malonic and caproic acids were isolated as decomposition products, whereas succinic and caproic acids were isolated from the decomposition of the ozonide of diheptynylethane, a γ-acetylenic compound.

$$CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_4CH_3 \rightarrow CH_3(CH_2)_4COOH + HOOCCH_2COOH + CH_3(CH_2)_4COOH$$

$$CH_3(CH_2)_4C{\equiv}CCH_2CH_2C{\equiv}C(CH_2)_4CH_3 \rightarrow CH_3(CH_2)_4COOH + HOOCCH_2CH_2COOH + CH_3(CH_2)_4COOH$$

It was by ozonization of the unknown compound obtained by treating the enol methyl ether (XLV) of 2,4,6-trimethylbenzoylacetonitrile (45) with phenylmagnesium bromide that the first insight into its correct structure was obtained. The isolation of isodurylic acid, benzoic acid, and a small amount of mesityl phenyl diketone (XLVI) suggested that the unknown ketone might be benzoylmesitylacetylene (XLVII), which was later proved by synthesis to be correct. Mesityl phenyl triketone would be expected as a product of the action of ozone, and the diketone was known to be a product of the decomposition of the triketone (46).



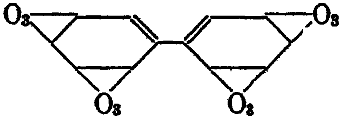
$$C_9H_{11}C{=}\overset{\overset{\displaystyle OCH_3}{|}}{C}HCN$$

XLV

$$\underset{\text{XLVII}}{C_9H_{11}C{\equiv}CCOC_6H_5} \longrightarrow C_9H_{11}COCOCOC_6H_5 \longrightarrow \underset{\text{XLVI}}{C_9H_{11}COCOC_6H_5}$$

The solution of the problem of the stereochemical configuration of various compounds has been aided by ozonolysis in certain cases. The geometric isomerism of oleic and elaidic acids was proven by Harries (72) by the quantitative identity of the products obtained on ozonization. In the same way, the stereoisomerism of erucic and brassidic acids, fumaric and maleic acids (61), and crotonic and isocrotonic acids (52) was shown to be correct.

Although benzene had been observed to form a triozonide, in accordance with the Kekulé formula, biphenyl formed only a tetraozonide. Harries (52) suggested that the tetraozonide had formula XLVIII and that the non-addition of ozone to the double bonds in the 1- and 1′-positions was due to steric hindrance.

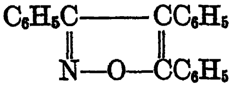


XLVIII

XLIX
1,1′-Bicyclohexenyl

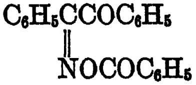
Because of the difficulty of preparing the ozonide, the products formed on decomposition with water have not been identified. Noller (116) suggested that it should be possible to determine whether steric hindrance plays a rôle by studying compounds such as 1-phenyl-1-cyclohexene and 1,1′-bicyclohexenyl (XLIX) in which non-benzenoid double bonds occur in positions similar to those which are supposed to be sterically hindered in biphenyl. On ozonization, it was found that 1-phenyl-1-cyclohexene added 1 mole of ozone to the double bond in the cyclohexene ring and that 1,1′-bicyclohexenyl added ozone to both double bonds. This indicated that steric hindrance in the 1- and 1′-positions was not the factor involved in the failure of biphenyl to form a hexaozonide.

Until the discovery in 1921 of a method of determining the configuration of ketoximes which was entirely independent of the Beckmann rearrangement, the erroneous mechanism of Hantzsch (51) had been almost universally accepted. In a study of triphenylisoxazole (L) Meisenheimer (108) found that this compound furnished on ozonization the benzoate of a benzil monoxime. An examination of the formulas will show that if no shift in configuration has taken place after ring opening, this benzoate should have the configuration represented by formula LI. Two benzil monoximes were known, a high-melting or α-oxime and a low-melting or β-oxime. Beckmann (9), from an examination of the products which these two oximes furnished on rearrangement, and assuming a *cis*-shift to have taken place on rearranging, had assigned to the α-oxime the configuration LII and to the β-oxime the configuration LIII.



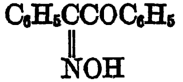
L

Triphenylisoxazole



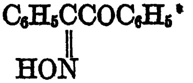
$$C_6H_5\underset{\substack{\| \\ NOCOC_6H_5}}{C}COC_6H_5$$

LI



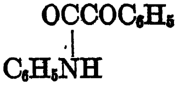
$$C_6H_5\underset{\substack{\| \\ NOH}}{C}COC_6H_5$$

LII



$$C_6H_5\underset{\substack{\| \\ HON}}{C}COC_6H_5$$

LIII

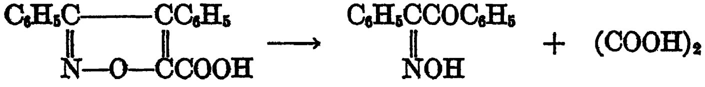


$$O\underset{\substack{| \\ C_6H_5NH}}{C}COC_6H_5$$

LIV

It is obvious from a comparison of formulas LI and LII that Meisenheimer's product from the ozonization of triphenylisoxazole should be the benzoate of the α-monoxime. Actually, that product proved to be the benzoate of the β-monoxime. It followed therefore that the rearrangement involved not a *cis*- but a *trans*-shift.

The ozonization of 3,4-diphenylisoxazole-5-carboxylic acid (LV) by Kohler (96) was of particular importance, for the reaction did not furnish a derivative of a benzil monoxime, but yielded directly the β-monoxime of benzil (LII).



LV

3,4-Diphenylisoxazole-5-carboxylic acid

LII

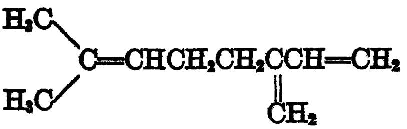
Benzil β-monoxime

By confirming the configuration LII assigned to the β-monoxime of benzil by Meisenheimer, this work strengthened the conclusion that the rearrangement of this β-monoxime involved a *trans*-shift. A final confirmation of configuration LII for the β-monoxime of benzil was afforded by the ozonization of 3,4-diphenyl-5-*p*-bromophenylisoxazole, which furnished the *p*-bromobenzoate of β-benzil monoxime (97).

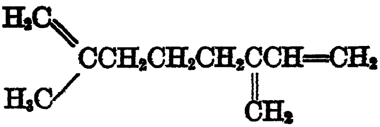
One of the earliest and most successful applications of the ozone method was the partial elucidation of the structure of rubber. Harries and his students (62) clarified its general structure by isolating levulinaldehyde and levulinic acid as the principal products of ozonization. This established the recurrence of an isoprene unit in the molecule and the position of the double bond adjacent to the methyl group. Since no other products were identified, Harries favored a ring structure made up of recurrent isoprene units and discounted Weber's open-chain formula, as such a compound would have to yield other additional decomposition products. In 1931, Pummerer (120) repeated Harries' ozonization experiments on a quantitative basis and isolated levulinic products in an amount equal to 90 per cent of the theoretical. In addition, by more refined methods, it was possible to detect acetic acid in an amount equivalent to at least 2 per cent of the carbon skeleton. A small amount of pyruvic acid was also detected. As a result, although the ends of a chain cannot be identified, a chain structure cannot be excluded from among the possible formulas.

Probably the most numerous examples of the use of ozone for structural proof may be found in the field of terpene chemistry. One of the most obvious points of attack of these complicated substances is the carbon-to-carbon double bond, when present, and its location, as well as the constitution of adjoining structures in many cases, has been demonstrated clearly by the isolation and identification of the ozonide decomposition products. All of the investigators in this field, including Harries, Semmler, Wallach, Ruzicka, Simonsen, and many others, have utilized the reaction in various instances, of which only a few examples will be considered here.

A correlation of the results of several investigators led Semmler (137), in 1901, to suggest that myrcene, one of the simpler terpene hydrocarbons, was represented by either formula LVI or LVII.

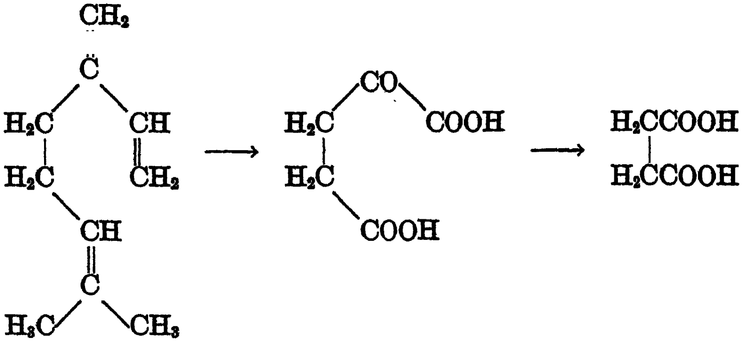


LVI
Myrcene

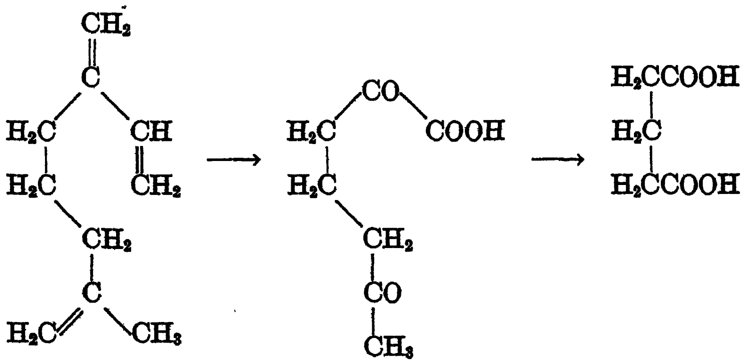


LVII

Recently Ruzicka and Stoll (130) showed conclusively that formula LVI correctly represents myrcene. The hydrocarbon was subjected to oxidation with ozone, and, after decomposition of the ozonide, followed by treatment with chromic acid and sodium hypobromite, succinic acid was obtained as the sole product of the reactions. If the hydrocarbon had formula LVII, the formation of glutaric acid would have been anticipated, as indicated in the schematic representation given below:

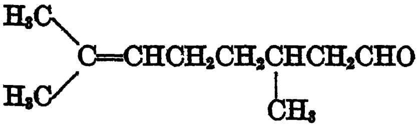


LVI

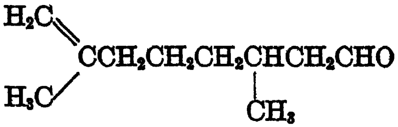


LVII

An interesting case of ozonization was the elaborate application of the reaction to the proof of structure of citronellal by Harries and his collaborators (63). Earlier work had indicated that this compound was a mixture of the aldehydes represented by formulas LVIII and LIX.



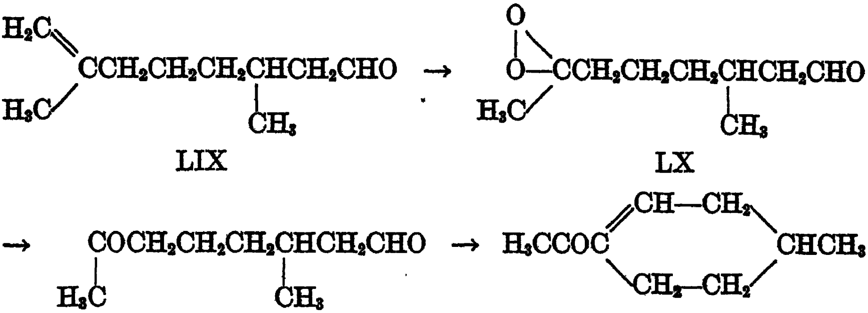
LVIII



LIX

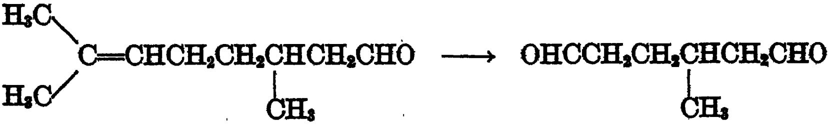
Harries, in collaboration with Wagner and Comberg, completely confirmed the view that citronellal was a mixture. From citronellal dimethyl acetal were obtained formic acid, acetone, the peroxide of methyloctanonal (LX), the cyclic ketone LXII, the semialdehyde of β-methyladipic acid

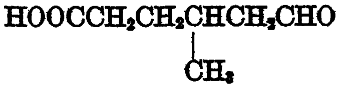
(LXIV or LXIVa), 5-methyl-Δ^1-cyclopentene-1-al (LXV), and 5-methyl-Δ^1-cyclopentene-1-carboxylic acid (LXVI). The separation of the peroxide LX established the presence of the aldehyde of formula LIX in the mixture. When this was decomposed by alkali the primary product, LXI, could not be isolated, since it passed immediately into the cyclic ketone LXII, a substance which had been described previously by Wallach and Evans (151).


LIX LX

LXI LXII

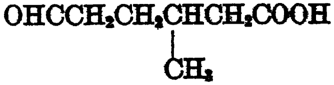
The other oxidation products were derived from the aldehyde of formula LVIII. The cyclopentenaldehyde (LXV) and acid (LXVI) were formed by the internal condensation of the primary oxidation product LXIII, the aldehyde LXV having been oxidized to the acid LXVI, while the dialdehyde LXIII also formed the half-aldehyde of β-methyladipic acid (LXIV or LXIVa). The yields of the various oxidation products showed the aldehyde to consist approximately of 60 per cent of LVIII and 40 per cent of LIX.


LVIII LXIII

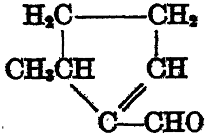

$HOOCCH_2CH_2CH(CH_3)CH_2CHO$

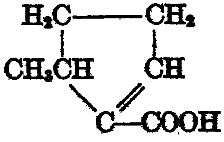
LXIV

or

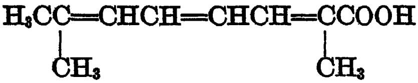

$OHCCH_2CH_2CH(CH_3)CH_2COOH$

LXIVa


LXV

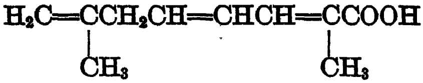

LXVI

Since the completion of these experiments, there has been much discussion as to the correct formulation of simple terpene derivatives like geraniol, citral, etc.: namely, as to whether an isopropenyl or an isopropylidene group should be placed at the end of the chain. The majority of these substances have been oils, and it has been generally held that inseparable mixtures of substances containing these two groups were present. R. Kuhn and Roth (99), in 1932, estimated quantitatively on a micro scale the acetone formed in the ozonization of a number of substances containing the isopropylidene group, and found it to vary from 60 to 90 per cent of the theoretical value. In particular, the crystalline acid dehydrogeranic acid (LXVII or LXVIII) was studied, and here, in agreement with earlier observations (29), both acetone and formaldehyde were obtained, the yield of acetone amounting to 60 per cent of the theoretical value.



$H_3C\underset{CH_3}{C}{=}CHCH{=}CHCH{=}\underset{CH_3}{C}COOH$

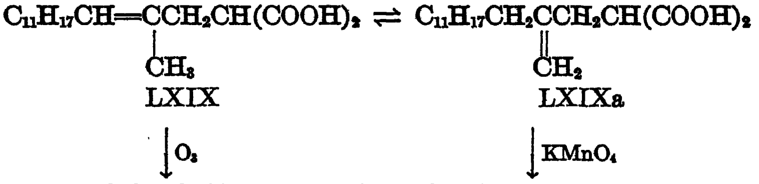
LXVII



$H_2C{=}\underset{CH_3}{C}CH_2CH{=}CHCH{=}\underset{CH_3}{C}COOH$

LXVIII

On the basis of comparisons of absorption spectra, Kuhn and Roth concluded that the acid was homogeneous and was represented by formula LXVII, but that the ozonization proceeded abnormally. According to Simonsen (138), a more satisfactory explanation has been provided by recent observations on the oxidation of α-santalylmalonic acid. When this acid, which is crystalline and readily purified, was ozonized, it yielded practically quantitatively tricycloekasantalal (LXX) or the corresponding acid. On the other hand, in alkaline solution, oxidation with potassium permanganate yielded the keto acid LXXI. To explain these results it was assumed that α-santalylmalonic acid exists in the tautomeric forms LXIX and LXIXa.



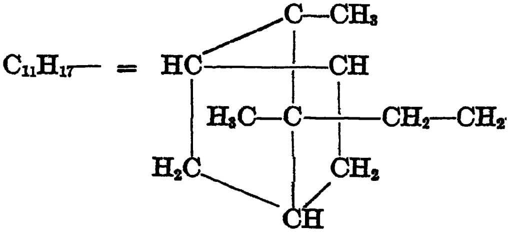
$C_{11}H_{17}CH{=}\underset{CH_3}{C}CH_2CH(COOH)_2 \rightleftharpoons C_{11}H_{17}CH_2\underset{\overset{\|}{CH_2}}{C}CH_2CH(COOH)_2$

LXIX　　LXIXa

$\downarrow O_3$　　$\downarrow KMnO_4$

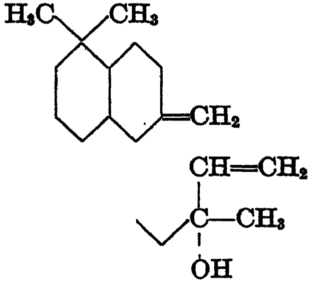
$C_{11}H_{17}CHO$　　$C_{11}H_{17}CH_2COCH_2CH(COOH)_2$

LXX　　LXXI

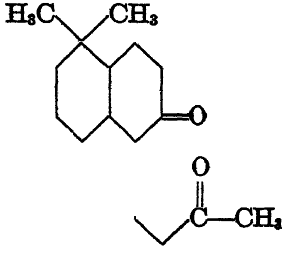


These represent the isopropenyl and isopropylidene forms of the acid, and tautomerism of this nature can provide an adequate explanation of Kuhn and Roth's results with dehydrogeranic acid. Simonsen considered it very probable that a similar tautomerism occurs also in the cases of geraniol, citral, etc.

Of the recent work with terpenes, the ozonization (77) of manoöl (LXXII) may be mentioned briefly. This is a diterpene alcohol excreted from the wood of *Dacrydium biforme*. Its structure was elucidated through characterization of the 1,5-diketone (LXXIII), isolated in about 50 per cent yield from decomposition of the diozonide.

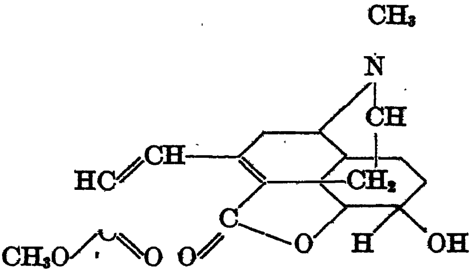


LXXII
Manoöl

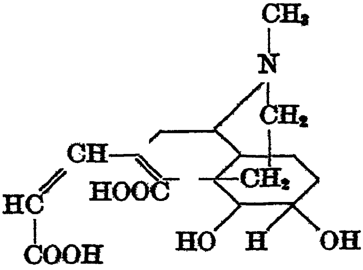


LXXIII

In the last fifteen years the application of the ozone degradation to various alkaloids has been improved, and in certain instances has yielded important results. By treatment of dihydrocodeine in formic acid solution with ozone, Speyer and Popp (140) obtained ozodihydrocodeine, which apparently resulted from scission of the 3,4-double linkage of the aromatic nucleus of dihydrocodeine. Ozodihydrocodeine contained two oxygen atoms more than the starting material, had neither aldehyde nor ketone properties, and was not phenolic. On the theory that the aromatic nucleus had been attacked, the substance was given formula LXXIV, which accounted well for its chemical behavior. By saponification, ozodihydrocodeine was converted to a dibasic acid, dihydromorphinic acid (LXXV).



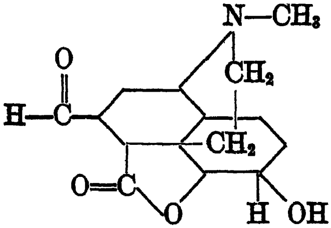
LXXIV
Ozodihydrocodeine



LXXV
Dihydromorphinic acid

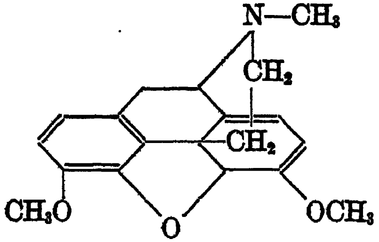
Additional evidence for the opening of the aromatic nucleus in this ozonization was found in the products from the treatment of dihydroethylmorphine with ozone; a homolog of ozodihydrocodeine, ozodihydroethylmorphine, was obtained (formula LXXIV, with $COOC_2H_5$ in place of $COOCH_3$), which yielded the same dihydromorphinic acid (LXXV) on saponification. This degradation differed from previous reactions in that the original position of the nitrogen ring was undisturbed.

In a later paper, Speyer (141) showed that ozonolysis of the lactone-ester LXXIV removed three carbon atoms as glyoxylic acid ester to form codinal (LXXVI), which was identical with the end product obtained in the ozonization of morphine.

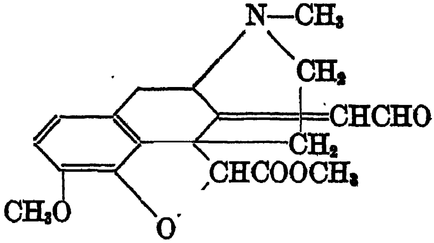


LXXVI
Codinal

In the case of thebaine, Wieland and Small (155) have brought to a successful conclusion the ozonolysis experiments begun by Pschorr and Einbeck in 1907 (119), to show that ozonization of thebaine results in the rupture of the 6,7-double bond, yielding the methyl ester of an acid containing an aldehyde group.

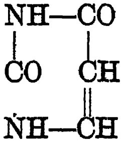


Thebaine

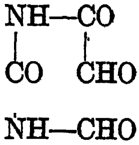


α-Thebaizone

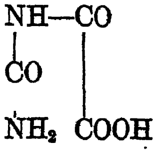
In 1931, Johnson and Flint (85), for the first time, investigated the behavior of pyrimidines toward ozone. It was found that uracil (LXXVII) and ozone interacted in glacial acetic acid at ordinary temperature to form chiefly formylglyoxylurea (LXXVIII) and oxaluric acid (LXXIX). In addition, part of the uracil molecule was completely broken down with formation of urea, oxalic acid, and formic acid. Formylglyoxylurea was the first member of its type to be described.



LXXVII
Uracil



LXXVIII
Formylglyoxylurea



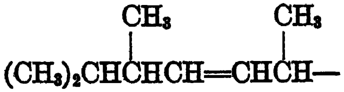
LXXIX
Oxaluric acid

In a second paper (86), the behavior of derivatives of uracil, including the 4-methyl-, 4-phenyl-5-bromo-, 5-nitro-, and 1,3-dimethyl-5-bromo-uracils and thymine, toward ozone was investigated with similar results. The authors stated: "The application of ozonization makes possible an improved technique for determining the structure of uracil compounds. The advantages gained experimentally become apparent when one is called upon to separate and identify the products of ozonization."

In the field of the azulenes, the blue substances which are constituents of certain essential oils, frequent applications of ozonolysis (4, 13, 109, 129) have been reported in attempts to prove the structure of these compounds. Experiments with the original substances and with partially hydrogenated compounds have been conducted. The products isolated and identified included formaldehyde, acetone, formic, acetic, oxalic, isobutyric, and α-methylglutaric acids. From these results it became evident (147) that further investigation of azulenes by oxidative degradation was unpromising, since only small fragments would be obtained, from which inferences could not be drawn concerning the original compounds. It is of interest that in this instance, as previously described, ozone proved to be of great value in synthesis, but of little use in degradation.

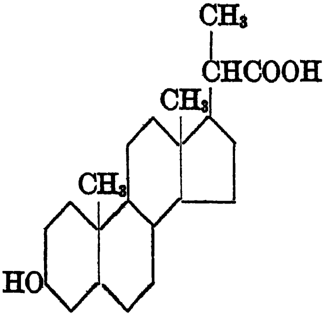
In the chemistry of the sterols, the early usage of ozone was fraught with difficulties, and led only to anomalous results. A number of papers were published (33, 34, 59) reporting the formation of an ozonide of cholesterol with a composition corresponding to the addition of about 2 moles of ozone, but no product could be identified on decomposition. The second mole of ozone added appears to have been due to a dehydration of the molecule during the initial action of ozone on the double bond, followed by addition of ozone to the bond so formed. The method was therefore abandoned in this connection. Recently, however, several important discoveries have been made by the ozonolysis of ergosterol and related compounds.

In 1932, Reindel and Kipphan (123) identified the aldehyde previously obtained (124) from the ozonide of ergosterol as methylisopropylacetaldehyde, a previously unexpected development, and the same aldehyde was also obtained from ergosterols B_1 and B_2, lumisterol, calciferol, and suprasterols I and II (50). All of these compounds therefore contained the same side chain,—



$$(CH_3)_2CH\overset{CH_3}{\overset{|}{C}}HCH{=}CH\overset{CH_3}{\overset{|}{C}}H—$$

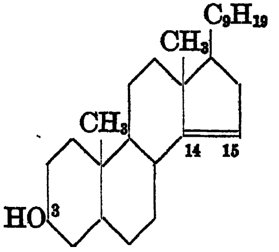
This was also found to be present in the maleic anhydride addition products of ergosterol, dihydroergosterol, and tachysterol, showing that the conjugated double bonds in these compounds were independent of the double bond between C_{22} and C_{23} in the side chain. Stigmasterol was later found to give ethylisopropylacetaldehyde on ozonization, in agreement with the formula $C_{29}H_{46}O$ assigned to it (49). In further work on stigmasterol, Fernholz (38) found that bromine could be added to the double bond situated in the nucleus, without affecting the one in the side chain. By ozonolysis of the acetate of this dibromide, a portion of the side chain was removed, and the product after debromination was reduced. Finally, hydrolysis yielded 3-hydroxybisnorallocholanic acid (LXXX), which on removal of the hydroxyl group gave bisnorallocholanic acid, a known compound. This sequence of operations proved that stigmasterol contained the same ring system as cholesterol and ergosterol.



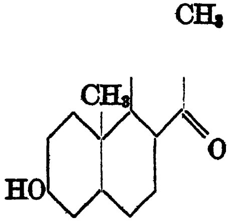
LXXX

3-Hydroxybisnorallocholanic acid

The exact position of the double bond in the nucleus of β-ergostenol (LXXXI) was proved by the use of ozone. Achtermann (2) ozonized the acetate, submitted the ozonide to reductive fission, followed by pyrolysis, and obtained a keto alcohol of the formula $C_{16}H_{26}O_2$ (LXXXII). This substance was fully characterized in 1935 by Laucht (101), who converted it by dehydrogenation with selenium into 2-methylphenanthrene. The other fragment of the pyrolysis, an α-unsaturated aldehyde, $C_{12}H_{22}O$, was isolated as the semicarbazone. These products could arise only from an initial ozonolysis between positions 14 and 15.



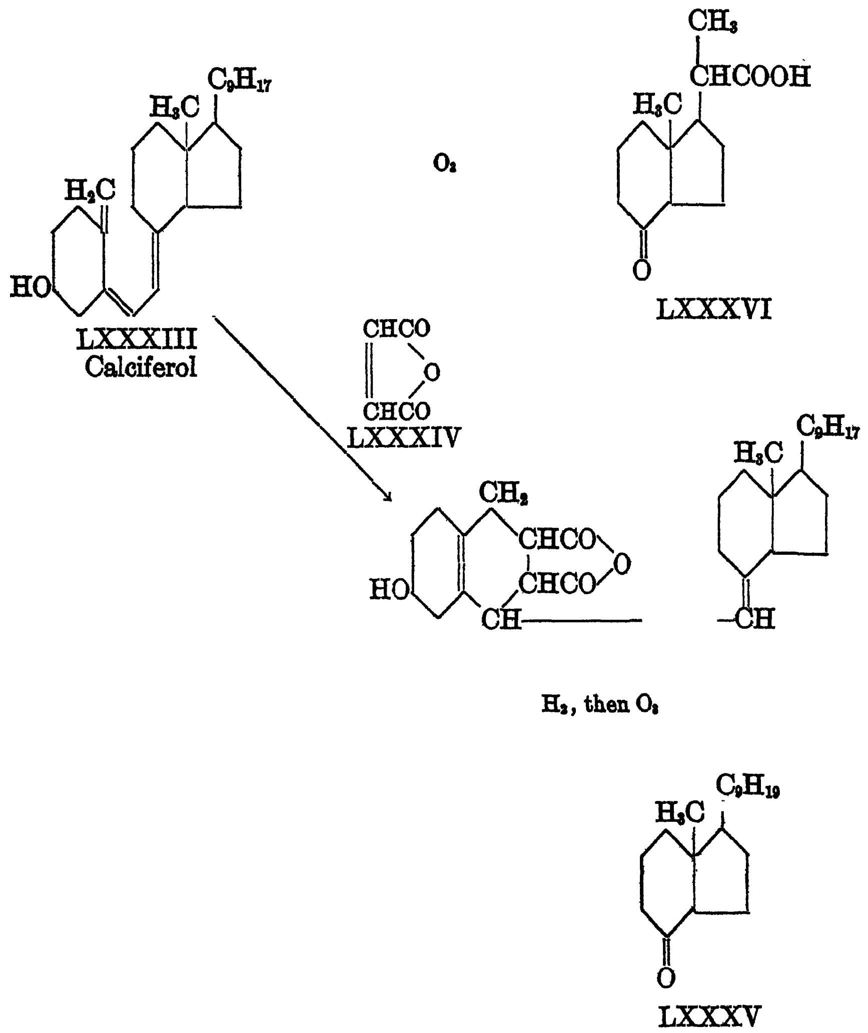
LXXXI
β-Ergostenol



LXXXII

In connection with the important antirachitic substance, vitamin D_2 or calciferol (LXXXIII), ozonolysis has also recently been of value. Windaus and Thiele (161) located the position of the double bonds in a series of experiments concerning the addition product of calciferol with maleic anhydride (LXXXIV). On ozonization of the dihydro derivative of the addition product there was obtained a saturated ketone which, from its composition ($C_{19}H_{34}O$, bicyclic), must have the structure shown in formula LXXXV. This observation established the presence of a double bond in the 7,8-position.

Further, Heilbron and his collaborators (74) ozonized vitamin D_2 and isolated as one product a keto acid, $C_{18}H_{20}O_3$ (LXXXVI), which must have resulted from the fission of the molecule at the C_7,C_8- and the C_{22},C_{23}-ethylenic linkages.



LXXXIII
Calciferol

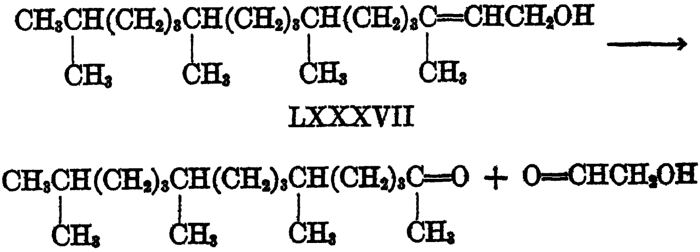
LXXXIV

LXXXVI

LXXXV

As a second product of ozonolysis, formaldehyde was isolated and characterized as the dimedon derivative. This established the presence of an exocyclic methylene group, as postulated by Windaus and Thiele (161), and removed any uncertainty in the evidence adduced by these investigators arising from the possibility of a rearrangement in the course of the Diels–Alder condensation. Windaus and Grundmann (159) confirmed these observations, and also obtained about 30 per cent of the calculated amount of formaldehyde, using ozone. Since ergosterol under similar conditions gave a few per cent of formic acid and a trace of formaldehyde, even though it contains no methylene group, Windaus regarded the isolation of the other oxidation products as providing the most reliable indication of the structure.

By the application of the ozone method Fischer and Löwenberg were able to deduce the structure of phytol, the alcoholic component of chlorophyll, and later proved the structure by synthesis. Willstätter and coworkers in 1911 (158) had obtained by oxidation of phytol a ketone which was considered to be $C_{17}H_{34}O$. Fischer and Löwenberg (40) reduced the ozonide of phytol, a C_{20} compound, using hydrogen and palladium–calcium carbonate as catalyst, and obtained glycolaldehyde and this same ketone, which must therefore be $C_{18}H_{36}O$. It was next assumed that phytol was built up of reduced isoprene units, and that its constitution might be 3,7,11,15-tetramethyl-Δ^2-hexadecen-1-ol (LXXXVII). This would give on hydrolysis of the ozonide a ketone, 6,10,14-trimethylpentadecan-2-one (LXXXVIII). The latter substance was synthesized from farnesol, and was found to be identical with the ketone derived from phytol. The constitution of phytol thus established was later confirmed by synthesis (44).



$$CH_3\underset{\displaystyle CH_3}{\overset{}{CH}}(CH_2)_3\underset{\displaystyle CH_3}{CH}(CH_2)_3\underset{\displaystyle CH_3}{CH}(CH_2)_3\underset{\displaystyle CH_3}{C}{=}CHCH_2OH \longrightarrow$$

LXXXVII

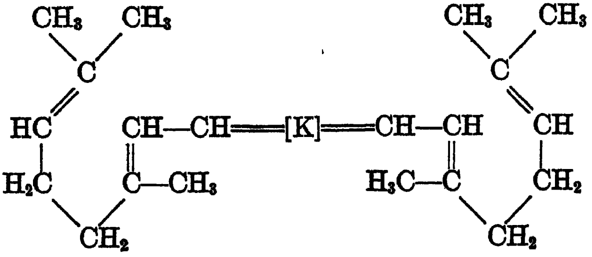
$$CH_3\underset{\displaystyle CH_3}{CH}(CH_2)_3\underset{\displaystyle CH_3}{CH}(CH_2)_3\underset{\displaystyle CH_3}{CH}(CH_2)_3\underset{\displaystyle CH_3}{C}{=}O + O{=}CHCH_2OH$$

LXXXVIII

The presence of the large number of double bonds characteristic of the carotenoids renders the latter open to attack by ozone at all these points, and decomposition of the ozonides so formed has resulted in a great variety of products. The determination of terminal groups has been the chief service of ozonolysis in this field.

Karrer and Bachmann (88) reported that ozonization of lycopene produced a large amount of acetaldehyde and acetic acid, and further the particularly important product, acetone. The isolation of the latter substance in an amount equal to 80 per cent of that calculated for two isopropylidene groups indicated that both ends of the molecule consisted of these groups, since neither geronic or isogeronic acid could be found. In addition, Strain (145) confirmed the earlier qualitative observation of

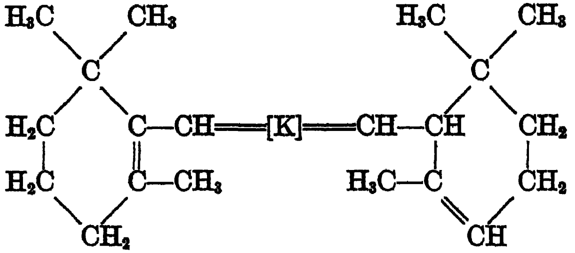
Karrer, by isolating from 0.90 to 1.32 moles of levulinic acid per mole of lycopene ozonized. These results substantiated the formula (LXXXIX) suggested for lycopene by Karrer and Bachmann.



LXXXIX
Lycopene
([K] = chain of four isoprene units)

Thus, lycopene is entirely acyclic, γ-carotene is acyclic at only one end, and α- and β-carotenes are cyclic at both ends.

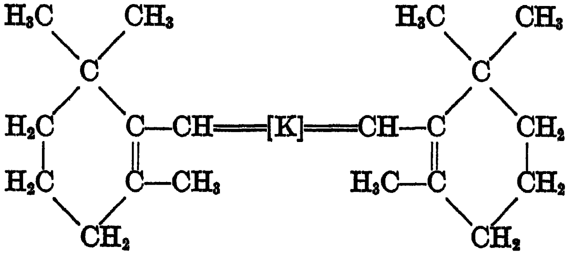
The constitution of α-carotene was proved conclusively in 1933 by the ozonolysis experiments of Karrer and coworkers (92), who isolated geronic acid and isogeronic acid by ozonization of pure α-carotene. Therefore the correct formula must be



XC
α-Carotene

This proof of the structure of α-carotene was of fundamental importance, since the simultaneous appearance of geronic and isogeronic acids as decomposition products proved the presence of two ionone carbon-ring systems in the carotenoids.

The ozonolysis of β-carotene (89) yielded much the same larger cleavage fragments as β-ionone. The observation that one molecule of β-carotene yielded two of geronic acid, whereas β-ionone gave only one (121), showed that β-carotene must contain two such ionone cycles. In addition, the isolation of glyoxal strengthened the evidence in support of Karrer's formula (XCI).

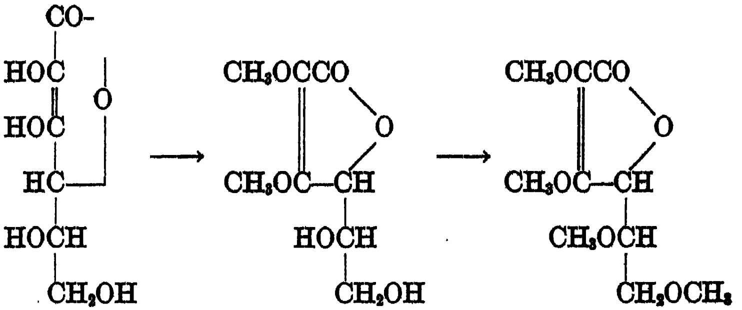


XCI
β-Carotene

Another important result of ozonolysis in this field was its application to vitamin A. The first light on the structure of this substance was the formation of geronic acid from it on ozonization (90), which indicated that it contained an unsubstituted β-ionone cycle.

The rapid solution of the ascorbic acid (vitamin C) problem has been one of the major achievements in the field of sugar chemistry, and in it ozonolysis has played its part by contributing a direct proof of the ring structure of the compound.

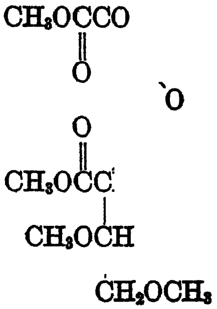
By the action of diazomethane on ascorbic acid (XCII), a dimethyl derivative (XCIII) was readily obtained (92, 112). Hirst and collaborators (76) found that both the methoxyl groups so introduced were enolic in origin. In addition, there were two other hydroxyl groups which could be methylated by Purdie's reagents, silver oxide and methyl iodide, giving tetramethylascorbic acid (XCIV). This substance reacted easily with ozone (76), two atoms



XCII
Ascorbic acid

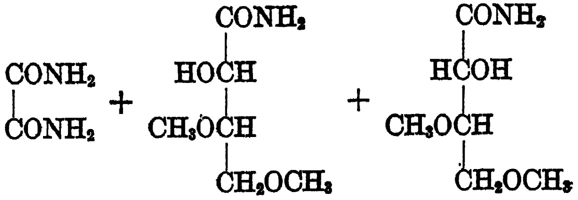
XCIII

XCIV
Tetramethylascorbic acid



$$\begin{array}{l} CH_3OCCO \\ \quad \| \\ \quad O \qquad \grave{}O \\ \quad O \\ \quad \| \\ CH_3OCC \\ \quad | \\ \; CH_3OCH \\ \qquad | \\ \qquad CH_2OCH_3 \end{array}$$

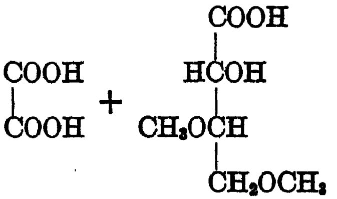
XCV



$$\begin{array}{c} CONH_2 \\ | \\ CONH_2 \end{array} + \begin{array}{c} CONH_2 \\ | \\ HOCH \\ | \\ CH_3OCH \\ | \\ CH_2OCH_3 \end{array} + \begin{array}{c} CONH_2 \\ | \\ HCOH \\ | \\ CH_3OCH \\ | \\ CH_2OCH_3 \end{array}$$

XCVI
3,4-Dimethyl-*l*-threonamide

XCVII
3,4-Dimethylerythronamide

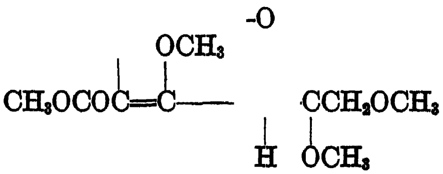


$$\begin{array}{c} COOH \\ | \\ COOH \end{array} + \begin{array}{c} COOH \\ | \\ HCOH \\ | \\ CH_3OCH \\ | \\ CH_2OCH_3 \end{array}$$

XCVIII
3,4-Dimethyl-*l*-threonic acid

of oxygen being added with formation of a neutral product, XCV, which was identified as methyl-3,4-dimethyl-*l*-threonate substituted in position 2 by a methyl oxalate residue. This reaction proceeded similarly to the ozonization of di-(*p*-nitrobenzoyl)dimethylascorbic acid studied by Micheel and Kraft (112). On treatment with methyl alcoholic ammonia the neutral ester XCV gave immediately oxamide and 3,4-dimethyl-*l*-threonamide (XCVI), together with a small quantity of the epimeric 3,4-dimethylerythronamide (XCVII). Hydrolysis of XCV with barium hydroxide gave barium oxalate and the barium salt of 3,4-dimethyl-*l*-threonic acid (XCVIII), again admixed with a small amount of 3,4-dimethyl-*l*-erythronic acid.

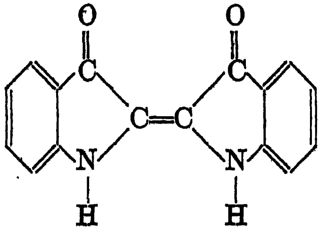
The reaction between tetramethylascorbic acid (XCIV) and ozone involved the addition of two oxygen atoms with formation of a neutral ester (XCV), and the breaking of the bond between the two carbon atoms which were united by a double linkage, but did not result in the formation of a substance containing a smaller number of carbon atoms. It followed, therefore, that a ring system was present in tetramethylascorbic acid and the nature of the reaction left open only two possibilities for the structure of XCIV, for which the alternative was as shown in formula XCIX, which contains a propylene oxide ring. The latter was inherently improbable, owing to the strained nature of the ring and the properties of dimethylascorbic acid.



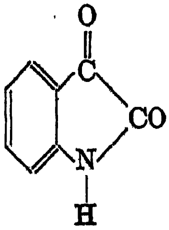
$$\overset{\text{-O}}{}\qquad CH_3OCO\overset{|}{C}{=}\overset{\overset{OCH_3}{|}}{C}\text{——}\quad \underset{\underset{H}{|}}{}\underset{\underset{OCH_3}{|}}{C}CH_2OCH_3$$

XCIX

Although indigo is one of the oldest known and most widely used organic compounds, the problem of its structure is still being investigated. The ozonization of indigo (C) reported in 1938 by van Alphen (3) gave, for the first time, a direct proof of von Baeyer's formula (7), advanced in 1883, which assumed that the two indole halves of the molecule are connected by a double bond between two carbon atoms. Previously, no direct evidence for this double bond had been found. The common reagents, including bromine, chlorine, and hydrogen, are not added by it and, although two geometrical isomers should exist, only one form of indigo is known. The isolation of isatin (CI) on decomposition of the ozonide of



C
Indigo



CI
Isatin

indigo with water has finally established the presence of an aliphatic double bond in the indigo structure.

X. THE LIMITS OF THE OZONE REACTION

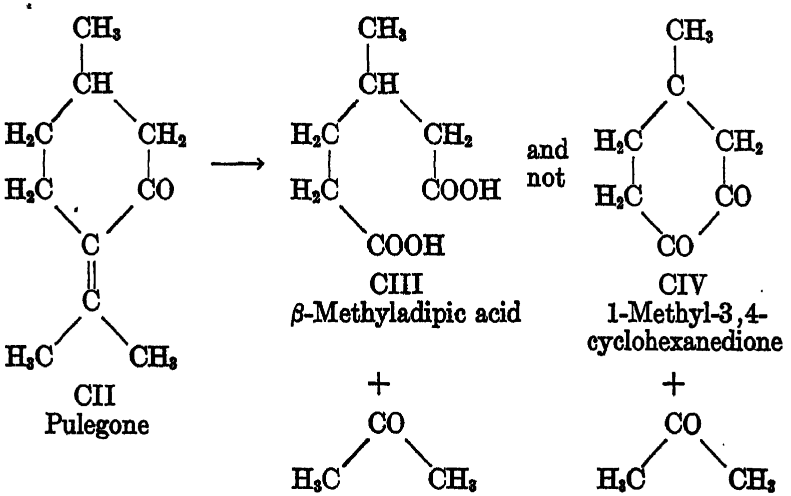
In the application of the ozonization method, there are certain limitations, based on past experience, which can be followed to advantage. Probably the most obvious disadvantage is the explosibility of certain ozonides, which may lead to the failure of an experiment. In almost every case, however, it is possible to avoid explosions either by exercising special precautions, such as working at low temperatures, or by carrying out the decomposition of the ozonide in solution.

There are, also, various structural configurations which have a marked effect on the course of the reaction. Ozone reacts more rapidly with isolated open-chain ethylenic linkages than with two or more conjugated double bonds or those present in aromatic ring systems, and it reacts more readily with a carbon-to-carbon than with a carbon-to-nitrogen double bond. Thus the ethylenic linkages in the side chain are attacked on ozonization of phenylated ethylenes, and the ozonization of triphenylisoxazole furnishes the benzoate of benzil monoxime. In general, however, the presence of a carbon-to-nitrogen double bond leads to complications which may render the results of ozonolysis inconclusive.

As regards the ozonization phase of the reaction, as distinguished from the decomposition of the ozonide, no general rules may be stated, since small changes in the structure of a molecule may require important modifications of procedure. In any case, nevertheless, over-ozonization is to be avoided. Ozone itself has seldom been observed to change the structure of a molecule, although, in one instance, Harries (70) reported the dehydration of a terpene alcohol with concentrated ozone, thereby obtaining a triozonide instead of the expected diozonide. The normal reaction ensued when weaker ozone was used.

Difficulties in the interpretation of the reaction may arise, owing to interaction, oxidation, or further decomposition of the primary decomposition products. An example may be cited in the case of the azulenes, previously described, where the small size of the products identified made it impossible to deduce the original structure.

Unstable aldehydes may either polymerize or decompose at the temperature necessary for the decomposition. On this account, the half-aldehyde of malonic acid could not be identified by Harries and Fonrobert (68), but instead acetaldehyde and carbon dioxide were found. Similarly, in the ozonization of pulegone (113) (CII) it was not possible to identify 1-methyl-3,4-cyclohexanedione (CIV), since β-methyladipic acid (CIII) was formed immediately.



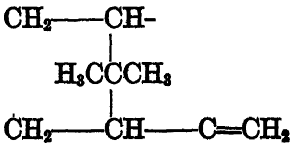
CII
Pulegone

CIII
β-Methyladipic acid

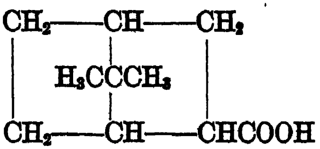
CIV
1-Methyl-3,4-cyclohexanedione

Fortunately it is often possible to prove the structure of the original compound from an identification of the secondary products formed, by a knowledge of the behavior of the primary products under similar experimental conditions.

One other unusual decomposition of an ozonide may be cited. Komppa and Roschier (98), in the ozonization of α-fenchene (CV), obtained a monobasic saturated acid CVI of which the structure was proved by synthesis.



CV
α-Fenchene



CVI

This represents the only case recorded in which the addition of ozone to a double bond has not resulted in fission of the molecule at this point.

Despite its limitations, the method has the decided advantage that it permits isolation of the primary cleavage products, for the excess oxidant, ozone, can be removed before the ozonide is cleaved. In oxidation with potassium permanganate and chromic acid the cleavage products are exposed to the action of the oxidant. In addition, no displacement of a double bond through addition of ozone and subsequent decomposition of the ozonide has ever been observed.

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THE CLAISEN REARRANGEMENT

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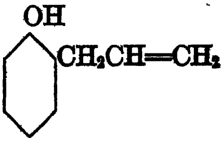
CONTENTS

I. INTRODUCTION

It was discovered by Claisen (23) in 1912 that allyl ethers of enols and phenols undergo a smooth rearrangement on heating, yielding the isomeric *C*-allyl compounds. This change, which can be illustrated by the conversion of allyl phenyl ether (I) to 2-allylphenol (II), has been investi-

$OCH_2CH{=}CH_2$

I
Allyl phenyl ether



II
2-Allylphenol

gated extensively by Claisen and other workers, and a large amount of information about it has been accumulated. The usefulness of the Claisen rearrangement in synthetic work, particularly in the synthesis of natural products, its application as a tool in the study of the bond structures of aromatic compounds, and its intrinsic interest as a molecular rearrangement have combined to stimulate a large amount of research.

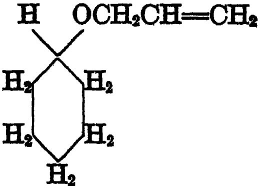
The present review will discuss the general topic of the Claisen rearrangement under three headings: (*1*) the nature and scope of the reaction, including the rearrangement of compounds analogous to allyl ethers but involving elements other than carbon and oxygen; (*2*) applications of the Claisen rearrangement as a tool in organic chemistry; and (*3*) possible mechanisms for the rearrangement.

II. NATURE AND SCOPE OF THE CLAISEN REARRANGEMENT

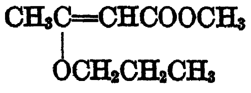
A. GENERAL CONDITIONS OF THE REARRANGEMENT

The types of compounds which undergo the Claisen rearrangement will be discussed in detail in later sections, but the general structural features necessary will be mentioned here.

The group of atoms $C{=}C{-}O{-}CH_2CH{=}CH_2$ must be present, in which the $C{=}C{-}O$ group may belong to an open-chain molecule or to an aromatic ring. The replacement of the hydrogens of the allyl group by alkyl or aryl groups does not, in general, hinder rearrangement, but this point will be discussed later. That the $C{=}C{-}O$ group is necessary is shown by Claisen's demonstration (21, page 97) that allyl cyclohexyl ether does not rearrange when refluxed. The necessity for the double bond in the allyl group is shown by the stability of methyl *O*-propylacetoacetate (23, 34) and *n*-propyl phenyl ether.



Allyl cyclohexyl ether



$$\underset{\displaystyle OCH_2CH_2CH_3}{CH_3C}{=}CHCOOCH_3$$

Methyl *o*-propylacetoacetate

OCH₂CH₂CH₃

n-Propyl phenyl ether

The benzyl phenyl ethers, $C_6H_5OCH_2C_6H_5$, contain the necessary atomic grouping, but they do not give the rearrangement under conditions (94, 26) comparable to those effective for the allyl ethers. Rearrangement can be forced under more drastic conditions, however (45, 11), but the product contains a large proportion of the para-compound.

As would be anticipated from the reactivity of allyl compounds in general, unsaturated ethers with the double bond in other than the β-position do not rearrange. Powell and Adams (94) showed that γ-butenyl phenyl ethers of the type $C_6H_5OCH_2CH_2CH{=}CH_2$ could be refluxed for 12 hr. without change, and that vinyl phenyl ether, $C_6H_5OCH{=}CH_2$, gave no rearrangement analogous to that of the allyl ethers. The same authors, and later Hurd and Cohen (49), showed that the double bond in the allyl group cannot be replaced by a triple bond, for the phenyl propargyl ethers, $C_6H_5OCH_2C{\equiv}CH$, do not rearrange on refluxing, although they give some phenol and other decomposition products.

The rearrangement of allyl aryl ethers is a process entirely distinct from the rearrangement of alkyl aryl, vinyl aryl, and benzyl aryl ethers (110); these ethers are usually rearranged in the presence of acidic catalysts and give a mixture of ortho- and para-products, frequently with considerable disubstitution. The allyl aryl ethers require no catalyst, almost invariably give no para rearrangement if an ortho-position is open, and give only traces of disubstitution products.

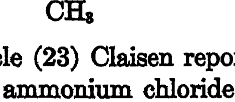
The following groups containing elements other than carbon and oxygen have been shown to give rearrangements analogous to the Claisen rearrangement (section F):

$CH_2{=}CHCH_2OCH{=}NR$ (109, 90, 16)
$CH_2{=}CHCH_2SC{=}C$ (51)
$CH_2{=}CHCH_2SC{\equiv}N$ (12, 17, 90a)
$CH_2{=}CHCH_2{-}C{-}C{=}C$ (31)

It will be noted that the relative positions of the two centers of unsaturation in these systems are the same as in the allyl ethers.

Compounds containing the following systems have been shown not to give a Claisen type of rearrangement on heating:

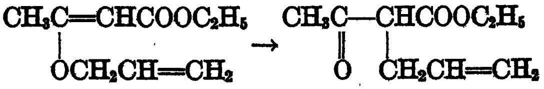
$CH_2{=}CHCH_2N{-}C{=}C$ (20)
$N{\equiv}CCH_2OC{=}C$ (94)



$$O{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_2OC{=}C$$

(106)

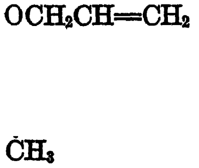
In his initial article (23) Claisen reported that *O*-allylacetoacetic ester, when distilled with ammonium chloride at atmospheric pressure, yielded the *C*-allylacetoacetic ester:



$$\underset{\displaystyle OCH_2CH{=}CH_2}{CH_3\underset{|}{C}}{=}CHCOOC_2H_5 \longrightarrow CH_3\underset{\displaystyle O}{\underset{\|}{C}}{-}\underset{\displaystyle CH_2CH{=}CH_2}{\underset{|}{C}H}COOC_2H_5$$

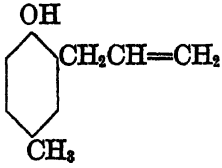
O-Allylacetoacetic ester   *C*-Allylacetoacetic ester

In extending his work to allyl ethers of phenols, Claisen found that the ammonium chloride catalyst was unnecessary and that high yields of the rearranged product were obtained by refluxing the ether for a short time under atmospheric pressure. Thus allyl 4-methylphenyl ether (I) gave an 80 per cent yield of 2-allyl-4-methylphenol (II) when refluxed without solvent for 1 hr. at atmospheric pressure (25, page 43).



I

Allyl 4-methylphenyl ether



II

2-Allyl-4-methylphenol

Since the rearrangement is markedly exothermic, the temperature of the liquid goes up during the reaction. The product of the reaction has a higher boiling point than the starting material, and therefore the progress of the reaction is accompanied by an increase in the boiling point, which ceases when the change is complete.

For simple allyl aryl ethers which have boiling points not too far above 200°C., this simple procedure of refluxing at atmospheric pressure until a constant boiling point is obtained is usually satisfactory. Claisen soon found that better yields were obtained in many cases when the ether was refluxed under diminished pressure, since undesirable side reactions were caused by refluxing at high temperatures (25, page 33). The same result was obtained more conveniently by mixing the ether with a solvent to act as diluent, the solvents most frequently employed being dimethylaniline (b.p. 193°C.) and diethylaniline (b.p. 215°C.). According to Claisen (21, page 72), better yields were obtained with these basic solvents than with indifferent hydrocarbon solvents (*cf.* 30). Recent kinetic studies of the rearrangement (70, 107, 69) have shown that dimethylaniline has only a negligible effect on the rate, and one is inclined to suspect that the superior solvent properties of the anilines are due to the fact that they can be separated from the product so readily by washing with dilute acid. Paraffin oil (21, page 111), tetralin (61), and kerosene (37) have been employed for the rearrangement with satisfactory results.

The reaction mixture in the case of phenols is usually worked up by removing the basic solvent, if present, by dilute mineral acid, taking up the residue in petroleum ether, and extracting with alkali to separate the phenolic product from the neutral by-products and starting material. When the phenols are highly substituted, especially the 2,6-disubstituted ones, their acidity may be so greatly diminished that they are practically insoluble in aqueous alkali; in such cases "Claisen's alkali" (21, page 96), prepared by dissolving 350 g. of potassium hydroxide in 250 cc. of water and diluting to 1 liter with methanol, has proved of great service in isolating weakly acidic phenols (21, 102, 37).

The use of a non-oxidizing atmosphere, such as hydrogen, carbon dioxide, or nitrogen, usually gives a better product (53). In working with 1,5-diallyloxyanthracene, Fieser and Lothrop (39) found that no pure product was obtained when the compound was heated in diethylaniline, but when the rearrangement was carried out in the presence of acetic anhydride and diethylaniline, the rearrangement product was readily isolated in the form of its diacetate. The very sensitive dihydroxy compound formed was protected from decomposition by acetylation to give the stable diacetate.

TABLE 1

Rearrangement of straight-chain ethers

COMPOUND*		REFERENCES
Ethyl *O*-allylacetoacetate.	Ethyl *C*-allylacetoacetate	(23, 22, 73)
Ethyl *O*-cinnamylacetoacetate.................	Ethyl *C*-(α-phenylallyl)acetoacetate	(73, 15)
	Ethyl *C*-cinnamylacetoacetate	(15)
O-Allylacetylacetone......	*C*-Allylacetylacetone	(23)
O-Allyloxymethylenecamphor....................	*C*-Allyloxymethylene camphor	(23)
Allyl vinyl ether..........	Allylacetaldehyde	(56)
Allyl α-methylvinyl ether.	Allylacetone	(56)
Allyl α-phenylvinyl ether.	Allylacetophenone	(56)
γ-Ethylallyl vinyl ether...	(α-Ethylallyl)acetaldehyde	(57)
	(α,γ-Dimethylallyl)acetaldehyde	(57)
2-Propenyl-4-propyl-6-methoxyphenyl..........	$1,2,4,6\text{-}C_6H_2(OH)(R)(C_3H_7)(OCH_3)$†	(28)
2-Propenyl-4,6-dichlorophenyl.................	$1,2,4,6\text{-}C_6H_2(OH)(R)(Cl)_2$†	(28)
2-Propenyl-4,6-dimethylphenyl.................	$1,2,4,6\text{-}C_6H_2(OH)(R)(CH_3)_2$†	(28)

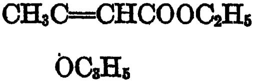
* In these tables, benzene compounds are named as derivatives of allyl phenyl ether, the words "allyl" and "ether" being omitted, except in the case of substituted allyl groups. Thus "4-methylphenyl" in the table refers to "allyl 4-methylphenyl ether." Ethers derived from polycyclic aromatic hydrocarbons and heterocyclic compounds are named as allyloxy derivatives of the nucleus in question: thus, "2-allyloxynaphthalene" instead of "allyl 2-naphthyl ether."

† R equals

$-CH{=}\underset{\substack{|\\ CH_3}}{C}CH_2CH{=}CH_2.$

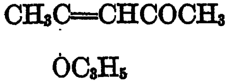
B. REARRANGEMENT OF OPEN-CHAIN COMPOUNDS

In his first report (23, 22), as mentioned before, Claisen stated that ethyl *O*-allylacetoacetate (I) and *O*-allylacetylacetone (II) on distillation with ammonium chloride gave the corresponding *C*-allyl derivatives in good yield (III from I and the corresponding compound from II). The *O*-allyl derivative of oxymethylenecamphor gave a similar rearrangement to the *C*-allyl compound, whose structure was proved by cleavage with alcoholic alkali to *C*-allylcamphor and formic acid:



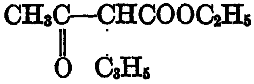
$$\mathrm{CH_3\underset{\substack{|\\ OC_3H_5}}{C}{=}CHCOOC_2H_5}$$

I
Ethyl
O-allylacetoacetate



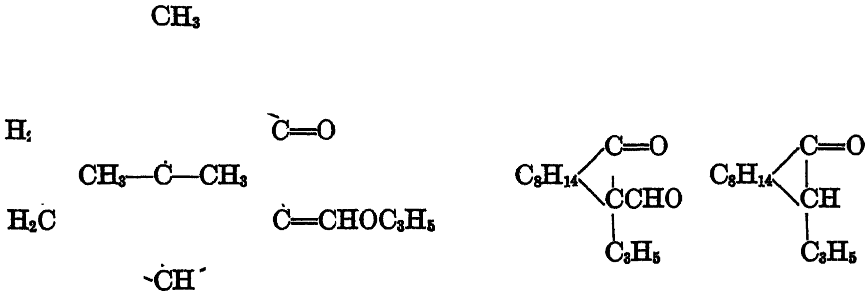
$$\mathrm{CH_3\underset{\substack{|\\ OC_3H_5}}{C}{=}CHCOCH_3}$$

II
O-Allylacetylacetone



$$\mathrm{CH_3\underset{\substack{\|\\ O}}{C}{-}\underset{\substack{|\\ C_3H_5}}{C}HCOOC_2H_5}$$

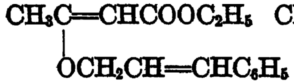
III
Ethyl
C-allylacetoacetate



C-Allylcamphor

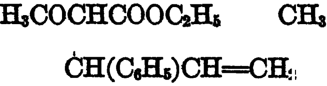
Claisen's paper gave no experimental details of his work with the enol ethers, but this was supplied later by Lauer and Kilburn (73), who showed that there was a slow rearrangement of I at 150–200°C., which was more rapid in the presence of ammonium chloride. The structure of the rearrangment product (III) was proved by comparison, through a solid derivative, with a known sample.

In the rearrangement of ethyl *O*-cinnamylacetoacetate (IV), Lauer and Kilburn (73) observed that the substituted allyl group after migration was attached by the γ-carbon, giving V, instead of being attached by the same carbon which was bonded to the oxygen in the ether. This phenomenon of γ-attachment is called inversion and is of very general occurrence.



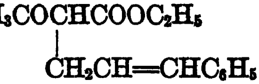
$$\mathrm{CH_3\underset{\substack{|\\ OCH_2CH=CHC_6H_5}}{C}{=}CHCOOC_2H_5}$$

IV
Ethyl
O-cinnamylacetoacetate



$$\mathrm{CH_3CO\underset{\substack{|\\ CH(C_6H_5)CH=CH_2}}{C}HCOOC_2H_5}$$

V

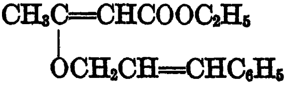


$$\mathrm{CH_3CO\underset{\substack{|\\ CH_2CH=CHC_6H_5}}{C}HCOOC_2H_5}$$

VI
Ethyl
C-cinnamylacetoacetate

Lauer and Kilburn carried out the rearrangement at 110°C. with ammonium chloride as catalyst and proved the structure of the product by reducing the double bond and forming the pyrazolone, which was identical with the pyrazolone prepared from compounds of known structure.

When ethyl *O*-cinnamylacetoacetate (IV) was heated for 4 hr. at 260°C., Bergmann and Corte (15) found that rearrangement took place without inversion; the product was shown to be VI by hydrolysis and decarboxylation to the ketone. When IV was hydrolyzed with alcoholic alkali, two products were obtained:



$$\begin{array}{l} CH_3C{=}CHCOOC_2H_5 \\ \;| \\ OCH_2CH{=}CHC_6H_5 \end{array} \rightarrow CH_2{=}CHCH(C_6H_5)CH_2COOH +$$

IV
Ethyl *O*-cinnamylaceto-
acetate

β-Phenyl-β-vinylpropionic
acid

$$CH_2{=}C(CH_3)OCH_2CH{=}CHC_6H_5$$

Cinnamyl α-methylvinyl ether

One was β-phenyl-β-vinylpropionic acid, which would be formed by rearrangement with inversion to give V, followed by acid cleavage. The second was cinnamyl α-methylvinyl ether, which would be formed by hydrolysis and decarboxylation of the starting material, without rearrangement. This compound is of considerable interest, in view of Hurd and Pollack's work (56) on the rearrangement of allyl vinyl ethers.

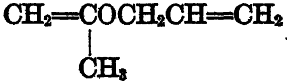
This work by Lauer and Bergmann confirms Claisen's results, and indicates that the inversion of cinnamyl enol ethers depends on the conditions employed.

The simplest compounds containing the C═C—O—C—C═C unit are the vinyl allyl ethers, which have been carefully investigated recently by Hurd and Pollack (56). Vinyl allyl ether itself rearranged cleanly at 255°C. in the gas phase:

$$CH_2{=}CHOCH_2CH{=}CH_2 \rightarrow CH_2{=}CHCH_2CH_2CHO$$

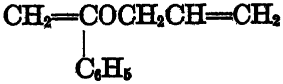
Vinyl allyl ether

No rearrangement took place at 215°C., and the reaction appeared to be about 50 per cent complete at 255°C. α-Methylvinyl allyl ether (VII) and α-phenylvinyl allyl ether (VIII) gave similar reactions,



$$\begin{array}{l} CH_2{=}COCH_2CH{=}CH_2 \\ \quad\;| \\ \quad CH_3 \end{array}$$

VII
α-Methylvinyl allyl
ether

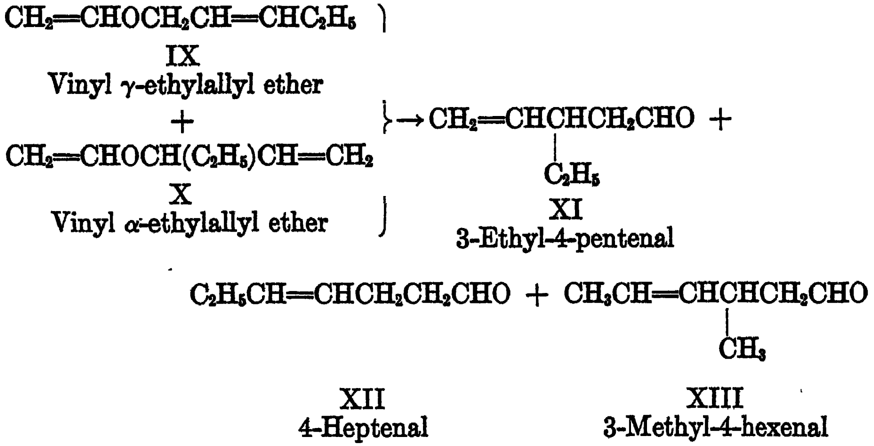


$$\begin{array}{l} CH_2{=}COCH_2CH{=}CH_2 \\ \quad\;| \\ \quad C_6H_5 \end{array}$$

VIII
α-Phenylvinyl allyl
ether

the former rearranging practically completely at 255°C. in the gas phase, and the latter after 15 min. refluxing at atmospheric pressure. The rate of rearrangement of these three compounds evidently increases in the order named.

In the rearrangement of a substituted vinyl allyl ether, Hurd and Pollack (57) found that inversion took place.

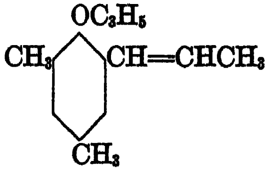


$$\left.\begin{matrix} \underset{\text{Vinyl }\gamma\text{-ethylallyl ether}}{\underset{\text{IX}}{CH_2{=}CHOCH_2CH{=}CHC_2H_5}} \\ + \\ \underset{\text{Vinyl }\alpha\text{-ethylallyl ether}}{\underset{\text{X}}{CH_2{=}CHOCH(C_2H_5)CH{=}CH_2}} \end{matrix}\right\} \rightarrow \underset{\text{3-Ethyl-4-pentenal}}{\underset{\text{XI}}{CH_2{=}CH\underset{\displaystyle C_2H_5}{\underset{|}{C}}HCH_2CHO}} +$$

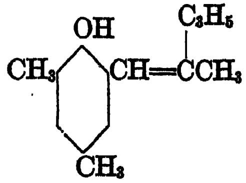
$$\underset{\text{4-Heptenal}}{\underset{\text{XII}}{C_2H_5CH{=}CHCH_2CH_2CHO}} + \underset{\text{3-Methyl-4-hexenal}}{\underset{\text{XIII}}{CH_3CH{=}CH\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CHO}}$$

The ether rearranged was a mixture of two allylic isomers, vinyl γ-ethylallyl ether (IX) and vinyl α-ethylallyl ether (X), consisting of 81 per cent of the former and 19 per cent of the latter; the figures are based on an analysis of the mixture of the isomeric bromides, 1-bromo-2-pentene and 3-bromo-1-pentene, from which the ethers were prepared, and the assumption was made that there were no allylic shifts involved in the preparation of the ethers. Rearrangement of the mixture of ethers was carried out at 255°C. in the gas phase, followed by heating in a sealed tube at 220°C. The product was a mixture of three compounds: (*1*) 3-ethyl-4-pentenal (XI, 76 per cent) formed from IX by inversion; (*2*) 4-heptenal (XII, 18 per cent) formed from X by inversion; (*3*) 3-methyl-4-hexenal (XIII, 4 per cent), an example of the anomalous type of rearrangement in which the substituted allyl group is attached by some carbon other than the γ-carbon after migration. Analyses of the mixtures of allylic isomers were carried out by ozonization and determination of the amounts of formic, acetic, and propionic acids formed.

A different type of rearrangement in which the allyl group migrates to an open-chain double bond was reported by Claisen and Tietze (28). They found that allyl phenyl ethers with a propenyl group in one ortho-position and substituents in the other ortho-position and in the para-position could be rearranged to phenols with the allyl group attached to the side chain. Thus, XIV gives XV in 37 per cent yield when refluxed



XIV



XV

under diminished pressure at 177°C. for 7 hr. Two other examples of this type of rearrangement were reported (57), and the reaction is interesting because it is analogous to the rearrangement of allyl phenyl ethers to the para-position of the benzene ring.

C. REARRANGEMENT OF ALLYL ARYL ETHERS TO THE ORTHO-POSITION

The most important case of the Claisen rearrangement is the formation of *o*-allylphenols from allyl aryl ethers. A search of the literature indicates that more than one hundred and fifty examples of this type of reaction are known (table 2), of which approximately one-third involve ethers with substituted allyl groups; the compounds studied involve aromatic and heterocyclic nuclei with a variety of substituents in the nucleus and side chain.

1. *General methods of preparing allyl aryl ethers*

The most general method of preparing allyl aryl ethers is that of Claisen (25, page 29), which consists in refluxing the phenol with allyl bromide and anhydrous potassium carbonate in acetone for several hours; allyl bromide may be replaced advantageously by allyl chloride and sodium iodide (85, 99). The method generally gives very good yields, but is unsatisfactory for weakly acidic phenols, which must be treated with sodium ethoxide in alcohol solution to obtain ether formation. The Claisen method is also unsatisfactory for phenolaldehydes, which condense with acetone in the presence of potassium carbonate. Substituted allyl chlorides and bromides usually can be used successfully (30, 58, 71, 10), although the yields are poorer, owing probably to *C*-alkylation.

The alkylation may be carried out in aqueous acetone with sodium hydroxide and allyl bromide (64), which gives a more rapid reaction and somewhat higher yields. The Williamson synthesis, using sodium ethoxide and allyl bromide in alcohol solution, is also more rapid than the acetone–potassium carbonate method and gives good results (25, 29, 26, 10).

TABLE 2

Rearrangement of allyl aryl ethers to the ortho-position

COMPOUND	PRODUCT	REFERENCES
	1. Benzene derivatives	
Phenyl	1,2-$C_6H_4(OH)(R)$*	(21, p. 79; 74, 1, 53, 59)
	2-Methyldihydrobenzofuran	(21, p. 79)
	1,2-$C_6H_4(OH)(CH_2CH(CH_3)OC_6H_4R)$	(59)
2-Methylphenyl	1,2,6-$C_6H_3(OH)(CH_3)(R)$	(25, p. 56)
3-Methylphenyl	1,2,3-$C_6H_3(OH)(R)(CH_3)$	(25, p. 58)
	1,3,6-$C_6H_3(OH)(CH_3)(R)$	
4-Methylphenyl	1,2,4-$C_6H_3(OH)(R)(CH_3)$	(25, p. 43; 64, 70)
2-Hydroxymethylphenyl	CH_2O and complete decomposition	(25, p. 106)
2-Allylphenyl	1,2,6-$C_6H_3(OH)(R)_2$	(21, p. 91)
2,4-Dimethylphenyl	1,2,4,6-$C_6H_2(OH)(R)(CH_3)_2$	(28, 69)
3,5-Dimethylphenyl	1,2,3,5-$C_6H_2(OH)(R)(CH_3)_2$	(2)
Mixture of 2-allyl-3-methylphenyl and 2-allyl-5-methylphenyl	1,3,x,x-$C_6H_2(OH)(CH_3)(R)_2$	(25, p. 58)
2-Allyl-4-methylphenyl	1,2,4,6-$C_6H_2(OH)(R)(CH_3)(R)$ (?)	(25, p. 45)
2-Propyl-4-methylphenyl	1,2,4,6-$C_6H_2(OH)(C_3H_7)(CH_3)(R)$	
	1,2,4-$C_6H_3(OH)(C_3H_7)(CH_3)$	(64)
2,3,5-Trimethylphenyl	1,2,3,5,6-$C_6H_1(OH)(CH_3)_3(R)$	(101, 99)
5-Allyloxy-6-methylindan	4-Allyl-5-hydroxy-6-methylindan	(79)
4,7-Dimethyl-5-allyloxyindan	4,7-Dimethyl-5-hydroxy-6-allylindan	(79)
4-(β-Carbomethoxyvinyl)phenyl	1,2,4-$C_6H_3(OH)(R)(CH{=}CHCOOCH_3)$	(86)
4-Chlorophenyl	1,2,4-$C_6H_3(OH)(R)(Cl)$	(25, p. 37)
2,4-Dichlorophenyl	1,2,4,6-$C_6H_2(OH)(Cl)_2(R)$	(28, 95)
2-Bromophenyl	1,2,6-$C_6H_3(OH)(Br)(R)$	(61)

4-Bromopheny	4-$C_6H_3(OH)(R)(Br)$	(25, p
2,4-Dibromophenyl	4,6-$C_6H_2(OH)(Br)_2(R)$	(61)
Dibromophenyl	3,5-$C_6H_2(OH)(R)(Br)_2$ Methyl-4,6-dibromodihyd an	(61)
2-Nitrophenyl	2,6-$C_6H_3(OH)(NO_2)(R)$	(25, p. 59)
4-Nitrophenyl	2,4-$C_6H_3(OH)(R)(NO_2)$	(25, p. 40)
4-A nophenyl	2,4-$C_6H_3(OH)(R)(NH_2)$	(21, p. 111
4-A taminophenyl	2,4-C_6H $(OH)(R)(NHC$ $CH_3)$	(21, p. 107
2,3,5-Trimethyl-4-formaminophenyl	2,3,4,5,6-$C_6(OH)(CH_3)_2$ $NHCHO)(CH_3)(R)$	(99)
2,3,5-Trimethyl-4-acetaminophenyl	2,3,4,5,6-$C_6(OH)(CH_3)_2$ $NHCOCH_3)(CH_3)(R$	(99)
2-Allyl-4-acetaminophenyl	2,4,6-C_6H $OH)(R)(NH$ $OCH_3)(R)$	(21, p. 112
4-(Phenylazo phenyl	4-$C_6H_3(OH$	(25, p. 42)
2-Hydroxyphenyl	6-$C_6H_3(OH$ R 2,4-$C_6H_3(OH)_2(R)$	(65, 9
2-Methoxyphenyl	2,6-$C_6H_3(OH)(OCH_3)($	(23, 8
2-Hydroxy-3-allylphenyl	2,3,6-C_6H OH $(R)_2$	(52)
2-Methoxy-4- llylphenyl	2,4,6-C_6H OH OCH	(25, p
2-Methoxy-4-propyl	2,4,6-$C_6H_2(OH$ $OCH_3)(C_3H_7)(R)$	(28
2-Methoxy-4(γ-hydroxypropyl)phenyl	2,4,6-$C_6H_2(OH$ $OCH_3)(CH_2CH_2CH_2OH$ R	(67
2-Allyloxyphenyl	ixture containing 1,2,3 6-$C_6H_2(OH)_2(R)_2$	(65, 52
3-Hydroxyphenyl	3,6-C_6H OH R	(52, 91
3-Methoxyphenyl	3,6-C_6H OH	(84
3-Hydroxy-4-nitrophenyl	3,4,6 $C_6H_2(OH)_2(NO_2)(R)$	(6)
3-Allyloxyphenyl	3,4,6-$C_6H_2(OH)_2(R)_2$	(52
3-Allyloxy-4,6-diallylphenyl	2,4,5,6-$C_6H_1(OH)(R)_2(OR)(R$	(52
4-Methoxyphenyl	2,4-$C_6H_3(OH)(R)(OCH_3)$	(84
4-Benzoyloxyphenyl	2,4-$C_6H_3(OH)(R)(OCOC_6H_5$	(43
4-Allyloxypheny	2,3,4-$C_6H_2(OH)(R)_2(OH)$ 2,4,5-$C_6H_2(OH)(R)(OH)(R$	(37
2,3-Methylenedioxyphenyl.	2,3 6-C $OH)(—OCH_2O$- R 2,3 4-C $OH)(—OCH_2O$- , R	(8) (7)
2-Allyloxy-3-methoxypheny	2,3 x,x-$C_6H_1(OH)_2(OCH_3)(R$	(55

TABLE 2—*Cont*

1. Benzene derivatives—*Continued*

2-Allyloxy-3-hydroxyphenyl (?)	1,2,3,x,x-$C_6H_1(OH)_3(R)_2$*	(55)
2-Aldehydophenyl	1,2,6-$C_6H_3(OH)(CHO)(R)$	(25, p. 96)
4-Aldehydophenyl	1,2,4-$C_6H_3(OH)(R)(CHO)$	(25, p. 107)
2-Allyl-4-aldehydophenyl	1,2,4,6-$C_6H_2(OH)(R)(CHO)(R)$	(25, p. 108)
2-Carbethoxyphenyl	1,2,6-$C_6H_3(OH)(COOC_2H_5)(R)$	(23)
	(For methyl ester)	(25, p. 70)
4-Carbethoxyphenyl	1,2,4-$C_6H_3(OH)(R)(COOC_2H_5)$	(25, p. 87; 74)
2-Allyl-4-carbethoxyphenyl	1,2,4,6-$C_6H_2(OH)(R)(COOC_2H_5)(R)$	(25, p. 89)
2-Methoxy-4-aldehydophenyl	1,2,4,6-$C_6H_2(OH)(OCH_3)(CHO)(R)$	(25, p. 116)
3-Hydroxy-4-aldehydophenyl	1,2,3,4-$C_6H_2(OH)(R)(OH)(CHO)$	(6)
3-Methoxy-4-aldehydophenyl	1,3,4,6-$C_6H_2(OH)(OCH_3)(CHO)(R)$	(6)
3-Hydroxy-4-acetylphenyl	1,2,3,4-$C_6H_2(OH)(R)(OH)(COCH_3)$	(5)
3-Methoxy-4-acetylphenyl	1,3,4,6-$C_6H_2(OH)(OCH_3)(COCH_3)(R)$	(5)
2-Allyl-3-hydroxy-4-acetylphenyl	1,2,3,4,6-$C_6H_1(OH)(R)(OH)(COCH_3)(R)$	(5)
3-Methoxy-4-acetyl-6-allylphenyl	1,2,3,4,6-$C_6H_1(OH)(R)(OCH_3)(COCH_3)(R)$	(5)
3-Hydroxy-4-propionylphenyl	1,2,3,4-$C_6H_2(OH)(R)(OH)(COC_2H_5)$	(6)
3-Methoxy-4-propionylphenyl	1,3,4,6-$C_6H_2(OH)(OCH_3)(COC_2H_5)(R)$	(6)
3-Acetyl-4-hydroxyphenyl	1,2,3,4-$C_6H_2(OH)(R)(COCH_3)(OH)$	(6)
3-Acetyl-4-methoxyphenyl	1,2,3,4-$C_6H_2(OH)(R)(COCH_3)(OCH_3)$	(6)

2. Derivatives of polycyclic aromatic hydrocarbons and heterocyclic compounds

1-Allyloxynaphthalene	1-Hydroxy-2-allylnaphthalene	(25, p. 61)
2-Allyloxynaphthalene	1-Allyl-2-hydroxynaphthalene	(23)
1-Allyl-2-allyloxynaphthalene	Unchanged by long heating	(23)
2-Allyloxy-1,4-naphthoquinone	2-Hydroxy-3-allyl-1,4-naphthoquinone	(35)
4-Allyloxy-1,2-naphthoquinone	2-Hydroxy-3-allyl-1,4-naphthoquinone	(35)
1-Allyloxy-3,7-dimethylnaphthalene	1-Hydroxy-2-allyl-3,7-dimethylnaphthalene	(37)

1-Allyloxy-5-methoxynaphthalene	1-Hydroxy-2-allyl-4-methoxynaphthalene	(46)
1,4-Diallyloxynaphthalene	1,4-Dihydroxy-2,3-diallylnaphthalene (as diacetate)	(37)
1,4-Diallyloxy-5,8-dihydronaphthalene	1,4-Dihydroxy-2,3-diallyl-5,8-dihydronaphthalene	(37)
2,6-Diallyloxynaphthalene	1,5-Diallyl-2,6-dihydroxynaphthalene	(38)
1,5-Diallyl-2,6-diallyloxynaphthalene	Only decomposition	(38)
2-Allyloxy-3-carbomethoxynaphthalene	1-Allyl-2-hydroxy-3-carbomethoxynaphthalene	(13)
4-Allyloxybiphenyl	3-Allyl-4-hydroxybiphenyl	(41)
2-Allyloxybiphenyl	2-Hydroxy-3-allylbiphenyl	(3)
2-Allyloxyphenanthrene	1-Allyl-2-hydroxyphenanthrene	(40)
3-Allyloxyphenanthrene	3-Hydroxy-4-allylphenanthrene	(40)
1-Methyl-7-isopropyl-9-allyloxyphenanthrene	1-Methyl-7-isopropyl-9-hydroxy-10-allylphenanthrene	(40)
1-Allyl-2-allyloxyphenanthrene	Decomposition only	(40)
2,6-Diallyloxyanthracene	1,5-Diallyl-2,6-dihydroxyanthracene (as diacetate)	(39)
1,5-Dimethyl-2,6-diallyloxyanthracene	Decomposition only	(39)
2-Allyloxyfluorene	1-Allyl-2-hydroxyfluorene and the 3-allyl isomer	(78)
1-Allyl-2-allyloxyfluorene and 3-allyl-2-allyloxyfluorene	1,3-Diallyl-2-hydroxyfluorene	(78)
1,2-Dimethyl-3-allyloxyfluorene	1,2-Dimethyl-3-hydroxy-4-allylfluorene	(78)
1,4-Dimethyl-3-allyloxyfluorene	1,4-Dimethyl-2-allyl-4-hydroxyfluorene	(78)
2-Allyloxyfluorenone	1-Allyl-2-hydroxyfluorenone and the 3-allyl isomer	(14)
1,6-Diallyloxydihydropleiadene	Decomposition only	(38)
2-Methyl-4-allyloxyquinoline	2-Methyl-3-allyl-4-hydroxyquinoline	(81)
2-Allyloxydibenzofuran	1-Allyl-2-hydroxydibenzofuran	(42)
4-Methyl-7-allyloxycoumarin	4-Methyl-7-hydroxy-8-allylcoumarin	(5)
2-Methyl-3-methoxy-7-allyloxychromone	2-Methyl-3-methoxy-7-hydroxy-8-allylchromone	(96)
2-Methyl-3-methoxy-7-allyloxy-8-allylchromone	2-Methyl-3-methoxy-6,8-diallyl-7-hydroxychromone	(96)
7-Allyloxyflavone	7-Hydroxy-8-allylflavone	(96)
7-Allyloxy-8-allylflavone	6,8-Diallyl-7-hydroxyflavone	(96)
3-Allyloxy-6-hydroxyfluoran	2-Allylfluorescein	(60)
3,6-Diallyloxyfluoran	2,7-Diallylfluorescein	(60)
Allyl 6-allyloxy-9-phenylfluorone-11-carboxylate	Allyl ester of 2-allylfluorescein	(60)

R eq —$CH_2CH{=}CH_2$

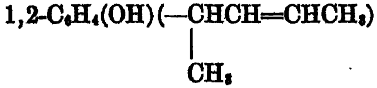
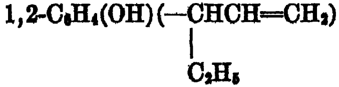
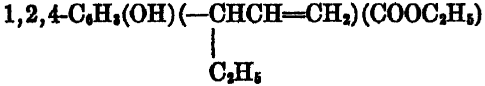
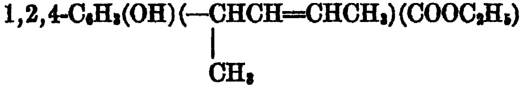
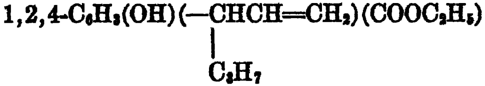
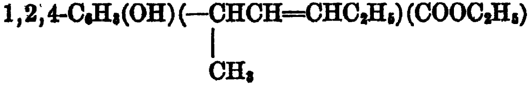
TABLE 2—*Continued*

COMPOUND	PRODUCT	REFERENCES
3. Rearrangements involving displacement of carbon monoxide and carbon dioxide from the ortho-position R equals $—CH_2CH{=}CH_2$		
2-Aldehydo-6-allylphenyl	$1,2,6\text{-}C_6H_3(OH)(R)_2$ and CO $1,2,4,6\text{-}C_6H_2(OH)(CHO)(R)_2$	(25, p. 102)
2-Aldehydo-4-allyl-6-methoxyphenyl	$1,2,4,6\text{-}C_6H_2(OH)(R)_2(OCH_3)$ and CO	(25, p. 115)
2-Aldehydo-6-methoxyphenyl	$1,2,6\text{-}C_6H_3(OH)(R)(OCH_3)$ $1,2,4,6\text{-}C_6H_2(OH)(R)(CHO)(OCH_3)$ $1,2,4,6\text{-}C_6H_2(OH)(CHO)(R)(OCH_3)$	(25, p. 112)
2-Carboxy-4,6-dichlorophenyl	$1,2,4,6\text{-}C_6H_2(OH)(R)(Cl)_2$	(21, p. 85)
2-Carboxy-6-methylphenyl	$1,2,6\text{-}C_6H_3(OH)(R)(CH_3)$ and CO_2 $1,2,4,6\text{-}C_6H_2(OH)(COOH)(R)(CH_3)$	(25, p. 83)
2-Carboxy-6-allylphenyl	$1,2,6\text{-}C_6H_3(OH)(R)_2$ and CO_2 $1,2,4,6\text{-}C_6H_2(OH)(COOH)(R)_2$	(25, p. 75)
2-Carboxy-4,6-diallylphenyl	$1,2,4,6\text{-}C_6H_2(OH)(R)_3$ and CO_2	(25, p. 79)
2-Carboxy-6-methoxyphenyl	$1,2,6\text{-}C_6H_3(OH)(R)(OCH_3)$ and CO_2 $1,2,4,6\text{-}C_6H_2(OH)(COOH)(R)(OCH_3)$	(21, p. 117)
4. Ethers with monosubstituted allyl groups		
β-Chloroallylphenyl	$1,2\text{-}C_6H_4(OH)(CH_2CCl{=}CH_2)$ 2-Methylbenzofuran	(62)
β-Bromoallyl phenyl	$1,2\text{-}C_6H_4(OH)(CH_2CBr{=}CH_2)$ (?)	(62, 18)
γ-Chloroallyl phenyl	Phenolic compounds	(62)
γ-Chloroallyl 4-methylphenyl	Polymeric products	(62)
γ-Bromoallyl phenyl	$BrCH_2CH{=}CHBr$ and phenol	(62)
α-Ethylallyl phenyl	$1,2\text{-}C_6H_4(OH)(CH_2CH{=}CHC_2H_5)$	(71)
α-Ethylallyl 4-carbethoxyphenyl	$1,2,4\text{-}C_6H_3(OH)(CH_2CH{=}CHC_2H_5)(COOC_2H_5)$	(77)
α-*n*-Propylallyl-4-carbethoxyphenyl	$1,2,4\text{-}C_6H_3(OH)(CH_2CH{=}CHC_3H_7)(COOC_2H_5)$	(75)

The following series of β-methylallyl ethers:†		
Phenyl	$1,2\text{-}C_6H_4(OH)(R)$	(10, 97)
4-Chlorophenyl	$1,2,4\text{-}C_6H_3(OH)(R)(Cl)$	(10)
2-Methylphenyl	$1,2,6\text{-}C_6H_3(OH)(CH_3)(R)$	(10)
3-Methylphenyl	$1,3,6\text{-}C_6H_3(OH)(CH_3)(R)$	(10)
4-Methylphenyl	$1,2,4\text{-}C_6H_3(OH)(R)(CH_3)$	(10)
2-(β-Methylallyl)phenyl	$1,2,6\text{-}C_6H_3(OH)(R)_2$	(10)
2,4-Dimethylphenyl	$1,2,4,6\text{-}C_6H_2(OH)(CH_3)_2(R)$	(10)
2,5-Dimethylphenyl	$1,2,5,6\text{-}C_6H_2(OH)(CH_3)_2(R)$	(10)
3,4-Dimethylphenyl	$1,3,4,6\text{-}C_6H_2(OH)(CH_3)_2(R)$	(10)
2-Isopropyl-5-methylphenyl	$1,2,5,6\text{-}C_6H_2(OH)(CH(CH_3)_2)(CH_3)(R)$	(10)
2-(β-Methylallyl)-4-methylphenyl	$1,2,4,6\text{-}C_6H_2(OH)(R)(CH_3)(R)$	(10)
2-(β-Methylallyl)-5-methylphenyl	$1,2,5,6\text{-}C_6H_2(OH)(R)(CH_3)(R)$	(10)
2-Methoxyphenyl	$1,2,6\text{-}C_6H_3(OH)(OCH_3)(R)$	(10)
3-(β-Methylallyloxy)phenyl	$1,3,4,6\text{-}C_6H_2(OH)_2(R)_2$	(10)
Cinnamyl phenyl	$1,2\text{-}C_6H_4(OH)(\text{—}\underset{\underset{\displaystyle C_6H_5}{\vert}}{C}HCH{=}CH_2)$	(29, 59)
Cinnamyl 4-methylphenyl	$1,2,4\text{-}C_6H_3(OH)(\text{—}\underset{\underset{\displaystyle C_6H_5}{\vert}}{C}HCH{=}CH_2)(CH_3)$	(29)
2-Cinnamyloxy-3-carbomethoxynaphthalene	1-(α-Phenylallyl)-2-hydroxy-3-carbomethoxynaphthalene	(13)
γ-Methylallyl phenyl	$1,2\text{-}C_6H_4(OH)(\text{—}\underset{\underset{\displaystyle CH_3}{\vert}}{C}HCH{=}CH_2)$	(19, 30, 76)
1-(γ-Methylallyloxy)naphthalene	1-Hydroxy-2-(α-methylallyl)naphthalene	(19, 30)
2-(γ-Methylallyloxy)-1,4-naphthoquinone	2-Hydroxy-3-(α-methylallyl)-1,4-naphthoquinone	(36)
4-(γ-Methylallyloxy)-1,2-naphthoquinone	Same compound as above	(36)

† R equals $\text{—}CH_2\underset{\underset{\displaystyle CH_3}{\vert}}{C}{=}CH_2$.

TABLE 2—*Continued*

COMPOUND	PRODUCT	REFERENCES
4. Ethers with monosubstituted allyl groups—*Continued*		
γ-Ethylallyl phenyl	 $1,2\text{-}C_6H_4(OH)(\text{—}\underset{CH_3}{\underset{\vert}{C}}HCH{=}CHCH_3)$	(71, 57, 58)
	 $1,2\text{-}C_6H_4(OH)(\text{—}\underset{C_2H_5}{\underset{\vert}{C}}HCH{=}CH_2)$	
γ-Ethylallyl 2-methylphenyl	$1,2,6\text{-}C_6H_3(OH)(CH_3)(C_5H_9)$	(58)
γ-Ethylallyl 4-carbethoxyphenyl	 $1,2,4\text{-}C_6H_3(OH)(\text{—}\underset{C_2H_5}{\underset{\vert}{C}}HCH{=}CH_2)(COOC_2H_5)$	(77)
	 $1,2,4\text{-}C_6H_3(OH)(\text{—}\underset{CH_3}{\underset{\vert}{C}}HCH{=}CHCH_3)(COOC_2H_5)$	
3-(γ-Ethylallyloxy)-6-hydroxyfluoran	2-Pentenylfluorescein	(60)
γ-(*n*-Propylallyl)phenyl	$1,2\text{-}C_6H_4(OH)(C_6H_{11})$	(54, 58)
γ-(*n*-Propylallyl) 2-methylphenyl	$1,2,6\text{-}C_6H_3(OH)(CH_3)(C_6H_{11})$	(58)
γ-(*n*-Propylallyl) 4-carbethoxyphenyl	 $1,2,4\text{-}C_6H_3(OH)(\text{—}\underset{C_3H_7}{\underset{\vert}{C}}HCH{=}CH_2)(COOC_2H_5)$	(75)
	 $1,2,4\text{-}C_6H_3(OH)(\text{—}\underset{CH_3}{\underset{\vert}{C}}HCH{=}CHC_2H_5)(COOC_2H_5)$	
3,6-Di-(γ-*n*-propylallyloxy)fluoran	2,7-Dihexenylfluorescein	(60)
γ-*n*-Butylallyl phenyl	C_6H_5OH and $1,2\text{-}C_6H_4(OH)(C_7H_{13})$	(58)

γ-*n*-Butylallyl 2-methylphenyl	$1,2\text{-}C_6H_4(OH)(CH_3)$ and $1,2,6\text{-}C_6H_3(OH)(CH_3)(C_7H_{13})$	(58)
γ-*n*-Propylallyl 2-(γ-*n*-propylallyloxy)-3-hydroxyphenyl (?)	$1,2,3,x,x\text{-}C_6H_1(OH)_2(C_6H_{11})_2$	(55)
γ-*n*-Butylallyl 2-(γ-*n*-butylallyloxy)-3-hydroxyphenyl (?)	$1,2,3,x,x\text{-}C_6H_1(OH)_2(C_7H_{13})_2$	(55)
Geranyl 2-hydroxyphenyl	$1,2,6\text{-}C_6H_3(OH)_2(C_{10}H_{17})$ (?)	(66)
1,4-Difarnesyloxynaphthalene	2,3-Difarnesyl-1,4-naphthohydroquinone (?) (as diacetate)	(80)

5. Ethers with disubstituted allyl groups

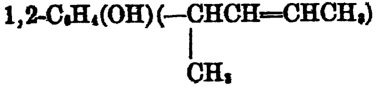
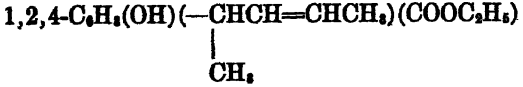
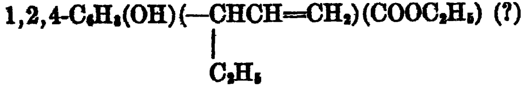
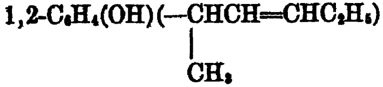
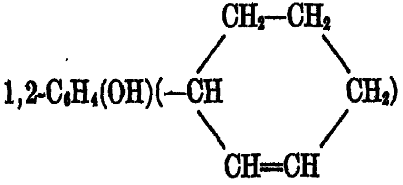
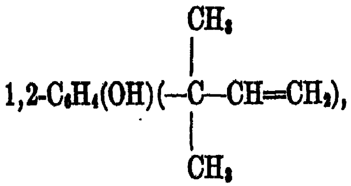
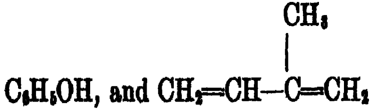
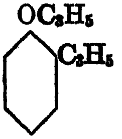
α,γ-Dimethylallyl phenyl	 $1,2\text{-}C_6H_4(OH)(\text{—}\underset{CH_3}{CH}CH{=}CHCH_3)$	(24, 50, 71)
α,γ-Dimethylallyl 4-carbethoxyphenyl	1,3-Pentadiene  $1,2,4\text{-}C_6H_3(OH)(\text{—}\underset{CH_3}{CH}CH{=}CHCH_3)(COOC_2H_5)$  $1,2,4\text{-}C_6H_3(OH)(\text{—}\underset{C_2H_5}{CH}CH{=}CH_2)(COOC_2H_5)$ (?)	(77)
α,γ-Ethylmethylallyl phenyl	 $1,2\text{-}C_6H_4(OH)(\text{—}\underset{CH_3}{CH}CH{=}CHC_2H_5)$ C_6H_5OH	(50, 58, 102)
α,γ-Ethylmethylallyl 2-methylphenyl	$1,2\text{-}C_6H_4(OH)(CH_3)$	(58)
α,γ-*n*-Propylmethylallyl phenyl	C_6H_5OH	(58, 63, 50)
α,γ-*n*-Propylmethylallyl 2-methylphenyl	$1,2\text{-}C_6H_4(OH)(CH_3)$	(58)
α,γ-*n*-Butylmethylallyl phenyl	C_6H_5OH	(58)
α,γ-*n*-Butylmethylallyl 2-methylphenyl	$1,2\text{-}C_6H_4(OH)(CH_3)$	(58)

TABLE 2—*Concluded*

COMPOUND	PRODUCT	REFERENCES
5. Ethers with disubstituted allyl groups—*Continued*		
Δ^2-Cyclohexenyl phenyl	Phenol, cyclohexadiene, hexahydrodibenzofuran, and 	(32)
γ,γ-Dimethylallyl phenyl	 $1,2\text{-}C_6H_4(OH)(\text{—}C(CH_3)_2\text{—}CH{=}CH_2)$,  C_6H_5OH, and $CH_2{=}CH\text{—}C(CH_3){=}CH_2$	(29, 30, 24)
$\alpha,\alpha,\gamma,\gamma$-Tetramethylallyl phenyl	C_6H_5OH and $CH_2{=}C(CH_3)CH{=}C(CH_3)_2$	(50)

Allylation of 2-hydroxy-1,4-naphthoquinone has been carried out by treating the silver salt in benzene with allyl bromide (35), which gives some *C*-alkylation as well as *O*-alkylation.

Varying amounts of *C*-alkylation are frequently observed; thus Claisen (21, page 78) found about 1 per cent of allyl *o*-allylphenyl ether (I) during the allylation of phenol by the potassium carbonate–acetone method, and



I
Allyl *o*-allylphenyl ether

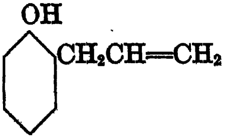
with the more active halides cinnamyl bromide and α,γ-dimethylallyl bromide the proportion of *C*-alkylation was greater (26). Smith, Ungnade, Lauer, and Leekley (102) obtained a complicated mixture of *C*- and *O*-alkylation products by treating phenol with 4-bromo-2-hexene and 4-chloro-2-hexene under the same conditions. Tarbell and Kincaid (107) obtained an appreciable amount of *C*-alkylation in treating 2,6-dimethylphenol with allyl bromide and sodium ethoxide in alcohol. Since, in general, the amount of *C*-alkylation is greatly increased by carrying out the alkylation on the sodium salt of the phenol in benzene (26), this method is unsuitable for the preparation of allyl ethers.

2. *Rearrangement of ethers with unsubstituted allyl groups*

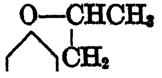
The simplest allyl aryl ether, allyl phenyl ether (I), rearranges to *o*-allylphenol (II) in practically quantitative yield when heated in an inert

$OCH_2CH{=}CH_2$

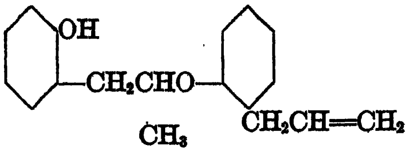
I
Allyl phenyl ether



II
o-Allylphenol



III
2-Methyldihydrobenzofuran



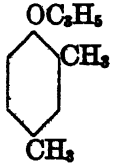
IV

atmosphere at 200°C. (21, page 79; 74, 1, 53); a small amount of 2-methyldihydrobenzofuran (III; 21, page 79) is formed concurrently. The addition of either alkali or acid does not seem to increase the rate of rearrangement, although acid does increase the amount of III; this is not surprising, since *o*-allylphenols are known to be changed to dihydrobenzofurans by acids (29). The rearrangement carried out without using an inert atmosphere gives a lower yield (34 per cent) and considerable amounts of polymeric material, including a dimer which probably has the structure indicated in formula IV (59).

Like nearly all ethers with a free ortho-position, allyl phenyl ether gives no detectable amount of para-product when rearranged (74). The limited number of ethers which give rearrangement to the para-position when the ortho-position is available will be discussed separately (page 525).

The rearrangement of allyl ethers in general gives high yields. Thus allyl 4-methylphenyl ether has been shown to give over 90 per cent of 2-allyl-4-methylphenol when heated in a nitrogen atmosphere for 13 hr. at 200°C. in sealed tubes (70); about 4 per cent of non-volatile material was obtained.

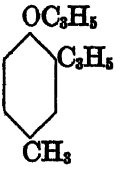
No very significant generalization can be made from the data available about the ease of rearrangement of allyl ethers of aromatic compounds. Although the number of examples is large, the information is almost entirely qualitative. From recent kinetic studies (70, 69) it is known that allyl 2,4-dimethylphenyl ether (V) rearranges about twice as rapidly as the monomethyl compound, allyl 4-methylphenyl ether, the former being completely rearranged by heating for 7 hr. at 193°C. Preliminary work (68) indicates that allyl *β*-naphthyl ether rearranges approximately twenty times as rapidly as V, the reaction being nearly complete in 25 min. at 174°C. The allyl ethers of 2-phenanthrol (VII) and 3-phenanthrol rearrange at 100°C. (40), which is the lowest temperature recorded for an ether with an unsubstituted allyl group. It seems likely that in numerous cases reported in the literature unnecessarily drastic conditions were employed and that better yields would be obtained at lower temperatures.



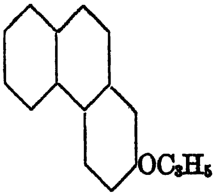
V

Allyl 2,4-dimethylphenyl ether

It appears from work of Claisen (25, pages 45, 58) that ethers with allyl groups in the nucleus, such as allyl 2-allyl-4-methylphenyl ether (VI) and the ethers from the isomeric allyl *m*-cresols, rearrange in poor yield, probably owing to polymerization through the nuclear allyl group.



VI
Allyl 2-allyl-4-methylphenyl ether



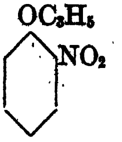
VII
Allyl ether of 2-phenanthrol

The list of allyloxy derivatives of hydrocarbons which have been rearranged (see table 2) includes ethers of benzene, toluene, xylene, allylbenzenes, naphthalene, anthracene, phenanthrene, fluorene, biphenyl, and hydrindene. The use of the Claisen rearrangement in determining bond structures of aromatic hydrocarbons will be discussed later. Among the heterocyclic compounds whose allyl ethers have been rearranged are fluorescein, quinaldine, flavone, chromone, dibenzofuran, and coumarin.

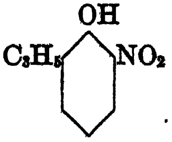
Allyl ethers of a long list of assorted derivatives of aromatic hydrocarbons have been rearranged, the substituents including hydroxyl, methoxyl, methylenedioxy, allyloxy (rearrangement involving migration of two allyl groups), aldehyde, carboxyl (*cf.* also section E for these two groups), acetyl, propionyl, γ-hydroxypropyl, carbethoxyl, β-carbomethoxyvinyl, halogen, nitro, amino, acetamino, and azo (table 2).

It is clear that the rearrangement takes place without regard for the nature of the substituents already present in the ring; there does not seem to be any more difficulty in effecting rearrangement of an ether with meta-directing groups in the ring than in rearranging an ether with the strongly ortho–para-directing hydroxyl or methoxyl groups.

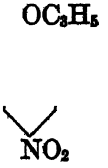
In fact, from the qualitative evidence available, it appears that the rearrangement of allyl 2-nitrophenyl ether (VIII) goes unusually readily, 73 per cent of the rearrangement product IX being obtained by heating for 5 hr. at 180°C. (25, page 59). The allyl 4-nitrophenyl ether (X), however, rearranges much less smoothly, 30 to 40 per cent yields being obtained by refluxing for 1.5 hr. in paraffin oil at 230°C. (25, page 40). The situation



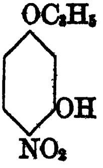
VIII
Allyl 2-nitrophenyl ether



IX



X
Allyl 4-nitrophenyl ether

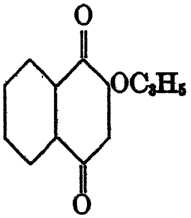


XI
Allyl 3-hydroxy-4-nitrophenyl ether

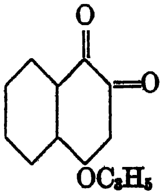
is complicated by the fact that allyl 3-hydroxy-4-nitrophenyl ether (XI) gives only 26 per cent rearrangement after 50 min. heating at 185°C., and 50 per cent of the starting material is recovered (6). On the basis of ordinary experience in aromatic substitution, it would be expected that the compounds VIII and X would rearrange with comparable ease, and that XI would rearrange more rapidly, if the ease of substitution of the nucleus were the decisive factor in the rearrangement.

It is obviously unsafe to draw many conclusions about relative rates of rearrangement from qualitative data on yields under various conditions, but it can be said that there is no correlation evident between the ease of rearrangement of the substituted ethers and the ease with which the same nuclei would react in typical aromatic substitution reactions. As pointed out previously, this may be because unnecessarily high temperatures were used in effecting rearrangements.

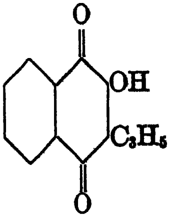
The allyl ethers of the isomeric hydroxynaphthoquinones (XII and XIII) rearrange to give the same compound (XIV) at relatively low temperatures, XII in 10 min. at 135°C. and XIII in a half-hour at 135–145°C. (35). The rapid reaction is probably connected with the fact that the allyl groups are attached to non-aromatic rings.



XII



XIII

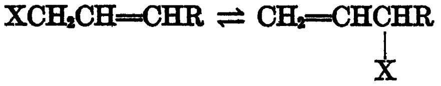


XIV

3. Rearrangement of ethers with substituted allyl groups; the anomalous rearrangement

Allyl ethers with substituents in the allyl group have been investigated in some detail, especially ethers of the types $ArOCH_2CH{=}CHR$ and $ArOCH(R)CH{=}CH_2$, where Ar is some aryl group and R is either alkyl or phenyl.

Work on ethers of this type is complicated by the fact that the halides necessary to prepare them are difficult to obtain pure, because of the ease with which the allylic rearrangement takes place:



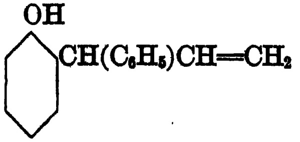
$$\underset{\text{I}}{XCH_2CH{=}CHR} \rightleftharpoons \underset{\text{II}}{CH_2{=}CH\underset{\displaystyle X}{\underset{|}{C}}HR}$$

The mobility of this equilibrium was demonstrated first by Winstein and Young (111) for the butenyl bromides (R equals CH_3), and the study was extended by Young and coworkers (112) to the pentenyl, hexenyl, and heptenyl bromides. Probably the alkenyl chlorides do not isomerize as readily as the bromides, but Young's work has demonstrated the necessity of careful proof of structure of compounds derived from halides of the type of I and II, since derivatives of both forms are usually present. Work done on allyl ethers of this type before this fact was realized is therefore open to question.

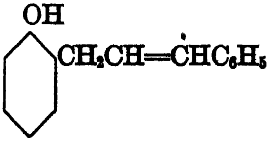
The cinnamyl ethers $ArOCH_2CH{=}CHC_6H_5$ are not open to this objection, since cinnamyl alcohol, $C_6H_5CH{=}CHCH_2OH$, gives only the corresponding bromide, without allylic rearrangement (87). Using cinnamyl phenyl ether (III), Claisen and Tietze (29) first showed that

$OCH_2CH{=}CHC_6H_5$

III
Cinnamyl phenyl ether



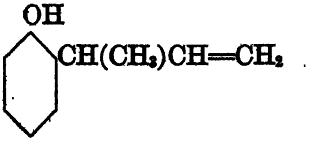
IV



V
o-Cinnamylphenol

rearrangement to the ortho-position was accompanied by inversion, because the product was different from the product obtained by direct *C*-cinnamylation of phenol. Barring an improbable allylic shift, the latter was *o*-cinnamylphenol (V) and the rearrangement product was IV, which means that the migrating group was attached to the ring by the γ-carbon atom. That IV is actually the sole product of the rearrangement of cinnamyl phenyl ether was proved later by Hurd and Schmerling (59), who ozonized the rearrangement product and showed the presence of formaldehyde and the absence of benzaldehyde.

Claisen and Tietze (30) showed by the same method that γ-methylallyl phenyl ether, $C_6H_5OCH_2CH{=}CHCH_3$, gave inversion on rearrangement; their crotyl bromide (I; R equals CH_3) evidently contained about 15 per cent of its allylic isomer (111), but that the rearrangement product was principally 2-(α-methylallyl)phenol (VI) was established by Lauer and coworkers (76, 72).

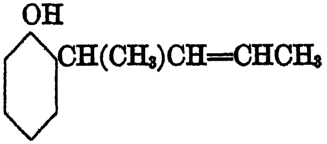


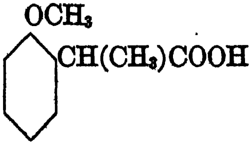
VI
2-(α-Methylallyl)phenol

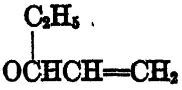
Rearrangement of many substituted allyl ethers has shown that in no case in rearrangement to the ortho-position is the substituted allyl group attached to the nucleus after rearrangement by the same carbon which was attached to the oxygen (*cf.* footnote, page 534); usually the attachment is by the γ-carbon atom (inversion), as shown by Claisen. The first example of anomalous rearrangement—attachment by other than the γ-carbon atom—was observed by Lauer and Filbert (71), who showed that rearrangement of γ-ethylallyl phenyl ether (VII) gave 2-(α,γ-dimethylallyl)phenol (VIII), whose structure was proved by ozonization to acetaldehyde and synthesis of the degradation product X (72). The formation of VIII shows that the allyl group is attached by the δ(or β)-carbon atom rather than the γ-carbon atom. When the allylic isomer of VII, α-ethylallyl phenyl ether (XI), was studied, the sole product obtained was 2-(γ-ethylallyl)phenol (XII), whose structure was proved by ozonization to propionaldehyde.

$OCH_2CH{=}CHCH_2CH_3$

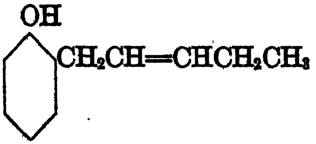
VII
γ-Ethylallyl phenyl ether

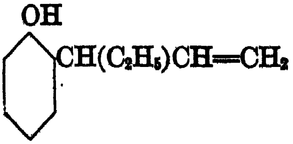

VIII
2-(α, γ-Dimethylallyl)phenol


X


$OCH(C_2H_5)CH{=}CH_2$

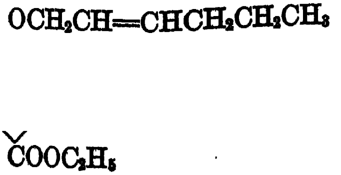
XI
α-Ethylallyl
phenyl ether


XII
2-(γ-Ethylallyl)phenol

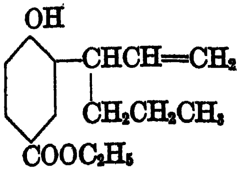

XIII
2-(α-Ethylallyl)phenol

This work was confirmed and extended by Hurd and Pollack (57), who showed that γ-ethylallyl phenyl ether (VII) yielded the normal product 2-(α-ethylallyl)phenol (XIII) in addition to the anomalous product VIII. From a mixture of 90 per cent of VII and 10 per cent of its allylic isomer (XI), they obtained 56 per cent of the normal product (XIII) and 42 per cent of the anomalous product (VIII).

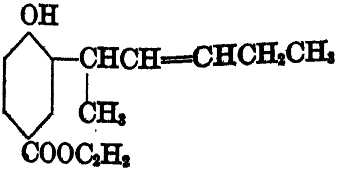
The question has been carefully investigated by Lauer and coworkers in recent papers (75, 77), using substituted allyl ethers of ethyl 4-hydroxybenzoate; this series is particularly well suited for such studies, because the 4-allyloxybenzoic acids are solids and the purity of the allylic isomers, such as XIV and XVII, can be assured by crystallization. Rearrangement of the γ-propylallyl ether (XIV) yielded the normal product (XV) and the anomalous product (XVI), the latter predominating by a ratio of two to one; the α-propylallyl ether (XVII) gave only the normal product (XVIII). The α-ethylallyl and γ-ethylallyl ethers in this series gave results similar to these (77); the former gave only the normal product and the latter gave both the normal and the anomalous products.


$OCH_2CH{=}CHCH_2CH_2CH_3 \; / \; COOC_2H_5$

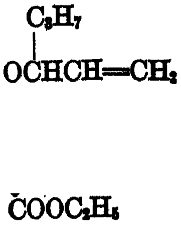
XIV



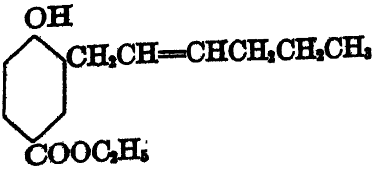
XV



XVI

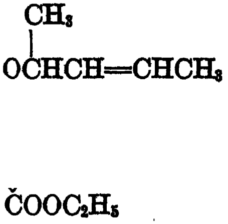

$\overset{C_3H_7}{|}$ $OCHCH{=}CH_2 \; / \; COOC_2H_5$

XVII

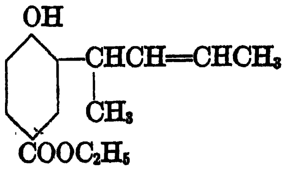


XVIII

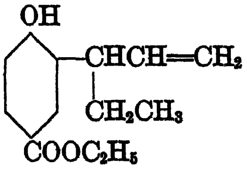
It is noteworthy that in the three cases investigated only the γ-substituted allyl ethers give the anomalous product, which in the ethyl series is formed by attachment through the δ(or β)-carbon, and in the propyl series by attachment through the ϵ(or β)-carbon. The α-substituted allyl ethers, however, give only the normal product. The only exception to this is α,γ-dimethylallyl 4-carbethoxyphenyl ether (XIX), which yields



XIX
α, γ-Dimethylallyl
4-carbethoxyphenyl ether



XX



XXI

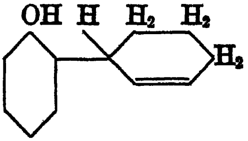
$CH_2{=}CHCH{=}CHCH_3$

XXII
1, 3-Pentadiene

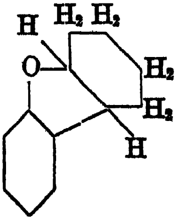
the expected product XX, but a few per cent of XXI is also formed, because formaldehyde is found in the ozonization product. The main product is 1,3-pentadiene (XXII), formed in 59 per cent yield by a cleavage of the carbon–oxygen link during rearrangement (77).

This cleavage of allyl ethers, with formation of a diene and a phenol, has been observed frequently (58, 54, 59, 50), and the tendency evidently increases with increasing substitution on the allyl group. Cornforth, Hughes, and Lions (32) found that cyclohexenyl phenyl ether on heating gave phenol and cyclohexadiene in 50 to 60 per cent yield, with 5 per cent of the rearrangement product XXIV and 15 per cent of hexahydrodibenzofuran formed from XXIV by ring closure. It would be of considerable interest to know if this reaction goes with inversion.

XXIII
Cyclohexenyl phenyl
ether

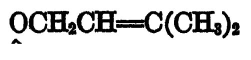


XXIV



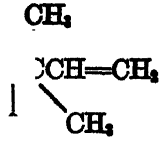
XXV
Hexahydrodibenzofuran

Claisen reported (24, 30), without giving experimental details, that γ,γ-dimethylallyl phenyl ether (XXVI) on pyrolysis gave phenol and isoprene, but that when heated with sodium carbonate it gave rearrangement. The structure of the ether was shown by reduction to isoamyl phenyl ether, and statements in the literature (48, 50) attributing a study of α,α-dimethylallyl phenyl ether (XXVII) to Claisen in this connection are erroneous. A more highly substituted allyl ether, α,α,γ,γ-tetramethylallyl phenyl ether (XXVIII), was shown by Hurd and Cohen (50) to give only the cleavage reaction, 33 per cent of hexadiene being obtained after 1 hr. at 160–170°C.



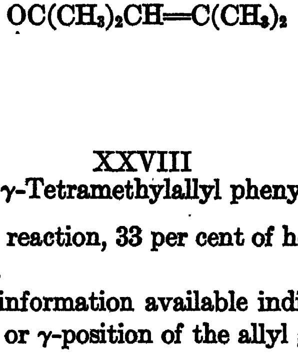
$OCH_2CH{=}C(CH_3)_2$

XXVI
γ, γ-Dimethylallyl phenyl ether



$$\overset{CH_3}{\underset{CH_3}{C}}CH{=}CH_2$$

XXVII
α, α-Dimethylallyl phenyl ether



$OC(CH_3)_2CH{=}C(CH_3)_2$

XXVIII
α, α, γ, γ-Tetramethylallyl phenyl ether

The small amount of information available indicates that introduction of alkyl groups in the α- or γ-position of the allyl group increases the rate of rearrangement. Smith and coworkers (102) found that α-ethyl-γ-methylallyl phenyl ether rearranged to the extent of 9.6 per cent in 24 hr. at 120°C. Fom this it seems likely that better yields would be obtained in general, if rearrangements were carried out at temperatures well below 200°C.

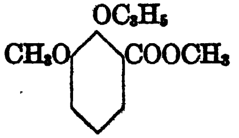
The β-methylallyl ethers are readily prepared from β-methylallyl chloride and phenols by standard methods (10, 97), but they present few points of interest. It has been found that β-methylallyl 4-methylphenyl ether rearranges at practically the same rate as the unsubstituted allyl 4-methylphenyl ether (69), and that the β-methyl group does not have the same complicating effect on the reaction as the α- or γ-methyl group.

Allyl aryl ethers with halogens in the allyl group rearrange very poorly; v. Braun, Kuhn, and Weismantel (18) found that β-bromoallyl phenyl ether gave 30 per cent of its rearrangement product, 2-$HOC_6H_4CH_2CBr{=}CH_2$, after heating in decalin at 215°C. for 1.5 hr. Fifty per cent was recovered unchanged and 20 per cent decomposed. Hurd and Webb (62) could not repeat this result, obtaining only intractable phenolic resins. They did obtain 24 per cent of the rearrangement product from the corresponding chloro compound after heating for 2 hr. at 216–223°C. From the γ-halogen ethers, such as $C_6H_5OCH_2CH{=}CHCl$, Hurd and Webb got no rearrangement product, but only decomposition and formation of phenol.

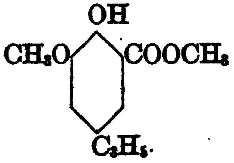
D. REARRANGEMENT OF ALLYL ARYL ETHERS TO THE PARA-POSITION

If both ortho-positions of an allyl aryl ether are blocked, the allyl group migrates to the para-position on heating in the usual manner (25, *passim*). The number of examples of this type of reaction is not large (table 3), but the rearrangement gives as good yields and goes as readily as the rearrangement to the ortho-position. Most of the compounds studied are derivatives of salicylic acid, with the other position ortho to the hydroxyl group occupied either by a methyl group (*o*-cresotic acid) or by a methoxyl group, but a few examples have two alkyl groups or two hydroxyl groups in the ortho-positions.

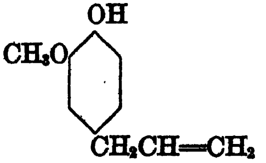
As an example of the facility of para rearrangement may be quoted the case of allyl 2-carbomethoxy-6-methoxyphenyl ether (I), which gave the rearrangement product II in almost quantitative yield on refluxing under diminished pressure for 45 min. (b.p. 201–212°C.) (21, page 118). The product was easily transformed, by hydrolysis and decarboxylation, into eugenol (III).



I
Allyl 2-carbomethoxy-6-methoxyphenyl ether

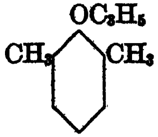


II

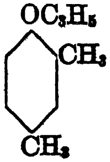


III
Eugenol

From the only pair which has been investigated quantitatively (107, 69), allyl 2,6-dimethylphenyl ether (IV) and allyl 2,4-dimethylphenyl



IV
Allyl 2,6-dimethylphenyl ether



V
Allyl 2,4-dimethylphenyl ether

TABLE 3

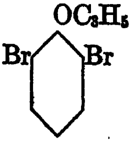
ngt t to tl para-p

1. Ethers with unsubstituted allyl groups; R equals $—CH_2CH{=}CH_2$. See also the section on rearrangement with displacement in table 2

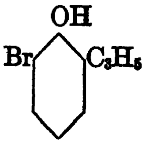
2,6-Dibromophenyl	1,2,6-C_6H_3(OH)(R)(Br) 1,2,4,6-C_6H_2(OH)(Br)(R)(Br)	(62, 95)
2-Bromo-6-methylphenyl	1,2,6-C_6H_3(OH)(Br)(CH_3) 1,2,4,6-C_6H_2(OH)(Br)(R)(CH_3)	(62)
2,6-Dimethylphenyl	1,2,4,6-C_6H_2(OH)(CH_3)(R)(CH_3)	(107)
2,6-Diallylphenyl	1,2,4,6-C_6H_2(OH)$(R)_3$	(21, p. 96)
2-Allyl-6-methoxyphenyl	1,2,4,6-C_6H_2(OH)$(R)_2$(OCH_3)	(25, p. 55)
2-Allyloxy-3,6-diallylphenyl	1,2,3,4,5,6-$C_6(OH)_2(R)_4$	(52)
2-Hydroxy-6-methoxyphenyl (?)	1,2,4,6-$C_6H_2(OH)_2$(R)(OCH_3)	(108)
2,6-Dimethoxyphenyl	1,2,4,6-C_6H_2(OH)(OCH_3)(R)(OCH_3)	(83, 44)
2,3-Dimethoxy-6-hydroxyphenyl	1,2,3,4,6-C_6H_1(OH)$(OCH_3)_2$(R)(OH)	(4)
2-Carbomethoxy-6-methylphenyl	1,2,4,6-C_6H_2(OH)($COOCH_3$)(R)(CH_3)	(25, p. 83)
2-Carbomethoxy-6-allylphenyl	1,2,4,6-C_6H_2(OH)($COOCH_3$)$(R)_2$	(25, p. 77)
2-Carbomethoxy-6-methoxyphenyl	1,2,4,6-C_6H_2(OH)($COOCH_3$)(R)(OCH_3)	(21, p. 118)
2. Ethers with substituted allyl groups		
α-Ethylallyl 2-carbomethoxy-6-methylphenyl	1,2,4,6-C_6H_2(OH)($COOCH_3$)($—CH_2CH{=}CHC_2H_5$)(CH_3)	(89)
β-Methylallyl 2-(β-methylallyl)-6-methylphenyl	1,2,4,6-C_6H_2(OH)$(—CH_2\underset{\underset{\displaystyle CH_3}{\vert}}{C}{=}CH_2)_2(CH_3)$	(10)
Cinnamyl 2-carbomethoxy-6-methylphenyl	1,2,4,6-C_6H_2(OH)($COOCH_3$)($—CH_2CH{=}CHC_6H_5$)(CH_3)	(90)
γ-Methylallyl 2-carbomethoxy-6-methylphenyl	1,2,4,6-C_6H_2(OH)($COOCH_3$)($—CH_2CH{=}CHCH_3$)(CH_3)	(90)
γ-Ethylallyl 2-carbomethoxy-6-methylphenyl	1,2,4,6-C_6H_2(OH)($COOCH_3$)($—CH_2CH{=}CHC_2H_5$)(CH_3)	(89)
γ,γ-Dimethylallyl 2-methoxyphenyl	1,2,4-C_6H_3(OH)(OCH_3)($—CH_2CH{=}C(CH_3)_2$)	(105)
Imperatorin	Alloimperatorin (see p. 527 for formulas)	(103, 104)
3. Rearrangements involving displacement		
2,6-Diallyl-4-aldehydophenyl	1,2,4,6-C_6H_2(OH)$(R)_3$ and CO	(25, p. 108)
2-Methoxy-4-aldehydo-6-allylphenyl	1,2,4,6-C_6H_2(OH)$(R)_2$(OCH_3) and CO	(25, p. 118)
2,6-Diallyl-4-carboxyphenyl	1,2,4,6-C_6H_2(OH)$(R)_3$ and CO_2	(25, p. 91)
2,6-Dimethoxy-4-carbomethoxyphenyl	1,2,4,6-C_6H_2(OH)(OCH_3)(R)(OCH_3) and CO_2	(44)

ether (V), it can be concluded that rearrangement to the para-position is not greatly different in rate from that to the ortho-position. The rearrangement of IV actually takes place a little more rapidly (about three and a half times) than rearrangement of V, and the rearrangement product from IV can be isolated in yields exceeding 90 per cent after heating for 7 hr. in sealed tubes at 172°C.

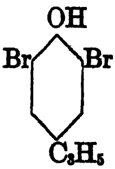
Rearrangement to the para-position goes poorly with two allyl groups or with bromine atoms in the ortho-positions; allyl 2,6-diallylphenyl ether gives a 50 per cent yield of 2,4,6-triallylphenol on refluxing with diethylaniline at 225–248°C. for a half-hour (21, page 96). Allyl 2,6-dibromophenyl ether (VI) was found by Hurd and Webb (62; *cf.* 95) to give a mixture of phenols (VII and VIII), the latter the expected product and



VI
Allyl 2,6-dibromophenyl ether



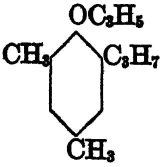
VII



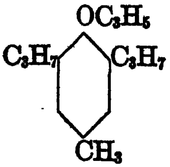
VIII

the former a result of a displacement of the bromine by the allyl group. Allyl 2-bromo-6-methylphenyl ether also gives a poor yield of rearrangement product.

If both of the ortho-positions and the para-position of an allyl phenyl ether are blocked by groups other than carboxyl or aldehyde, a complex decomposition reaction occurs on heating, but there is no migration of the allyl group to the meta-position. The carboxyl or aldehyde group if present is eliminated as carbon monoxide or carbon dioxide (section E), but with ester groups instead of free carboxyl, complete decomposition results (25, pages 79, 90). Thus Claisen and Tietze (28) found that allyl 2-propyl-4,6-dimethylphenyl ether (IX) yielded, on heating at 200–250°C.



IX
Allyl 2-propyl-4,6-dimethylphenyl ether



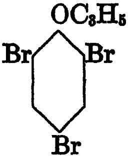
X

$(CH_2{=}CHCH_2)_2$

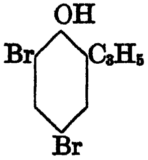
XI
Diallyl

for 15 min., some of the corresponding phenol, a gas (thought to be allene), and diallyl (XI). Recent work by Hurd and Yarnall (64) on an analogous compound (X) confirmed the formation of the phenol and diallyl, but showed that the gas evolved was propene.

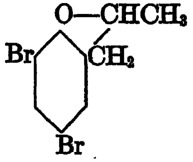
Hurd and Webb (62) obtained a mixture of phenolic and neutral products from allyl 2,4-dibromo-6-methylphenyl ether; allyl 2,4,6-tribromophenyl ether (XII) gave a 68 per cent yield of the *o*-allylphenol (XIII) and a small amount of the corresponding dihydrobenzofuran (XIV).



XII
Allyl 2,4,6-tribromophenyl ether

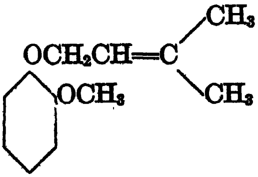


XIII

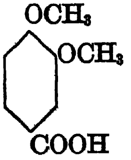


XIV

A few exceptional cases are known in which there is some migration of the allyl group to the para-position when there is also an open ortho-position. The first instance was found by Staudinger, Kreis, and Schilt (105), who rearranged γ,γ-dimethylallyl 2-methoxyphenyl ether (XV) and obtained, on methylation and oxidation, a small amount of veratric acid

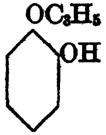


XV
γ,γ-Dimethylallyl 2-methoxyphenyl ether

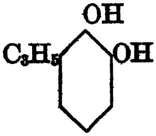


XVI
Veratric acid

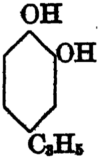
(XVI), showing that at least part of the product was the result of para rearrangement. Kawai (65) found that allyl 2-hydroxyphenyl ether (XVII) at 180–190°C. gave a mixture of products resulting from ortho and para rearrangement, whose structure was proved by methylation and



XVII
Allyl 2-hydroxyphenyl ether

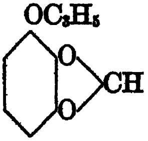


XVIII



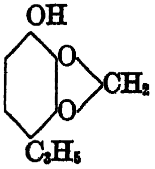
XIX

oxidation to the corresponding dimethoxybenzoic acids; the 1,2,4-compound (XIX) is regarded as a product of para rearrangement rather than meta, since the latter has never been observed. Perkin and Trikojus (93) showed that XVIII and XIX are formed in the ratio of five to four. Baker, Penfold, and Simonsen (7) have reported recently that allyl 2,3-methylenedioxyphenyl ether (XX) gives a mixture containing about 20 per cent of the para-isomer (XXI), whose structure was proved by methylation



XX

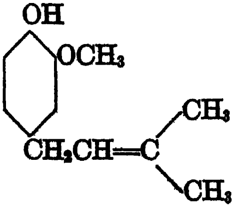
Allyl 2,3-methylenedioxyphenyl ether



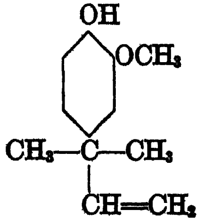
XXI

and oxidation to the substituted benzoic acid. It is noteworthy that each of these compounds giving the para and ortho rearrangement simultaneously is a polyhydroxy compound; perhaps the greater reactivity of the aromatic nucleus is the cause of the para migration. Other instances in which the migrating group goes to the para-position instead of displacing a carboxyl or aldehyde group from the ortho-position are discussed in section E.

Some information on the question of inversion of a substituted allyl group on migration to the para-position can be obtained from Staudinger's work, quoted above. The rearrangement product of XV must have been the one formed without inversion (XXII); the isomeric compound (XXIII) would not yield veratric acid (XVI) on methylation and oxidation, since,



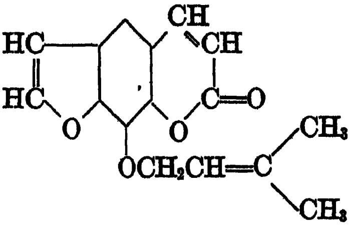
XXII



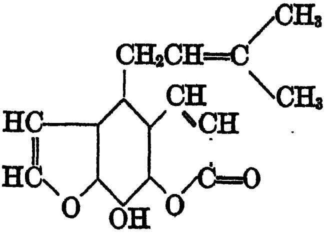
XXIII

as Smith and Prichard have shown (100), side chains such as the one in XXIII cannot be oxidized to carboxyl groups by permanganate. The possibility is not excluded that the product was a mixture of XXII and XXIII, but the positive evidence shows that XXII was present.

More clear-cut evidence on this point was furnished by Späth (104, 103), by showing that imperatorin (XXIV) was changed in 90 per cent

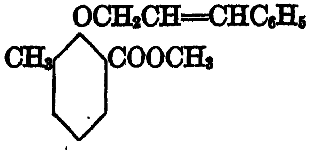


XXIV
Imperatorin

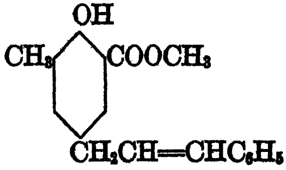


XXV
Alloimperatorin

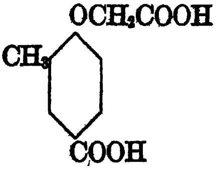
yield on heating for a few minutes at 200°C. to alloimperatorin (XXV); both substances yielded acetone on oxidation with chromic acid, and therefore contained the γ,γ-dimethylallyl group, which had rearranged without inversion. Mumm and Möller (90) observed that rearrangement of cinnamyl 2-carbomethoxy-6-methylphenyl ether (XXVI) also took place without inversion; proof that the rearrangement product had the



XXVI
Cinnamyl 2-carbomethoxy-6-methylphenyl ether



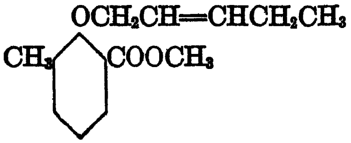
XXVII

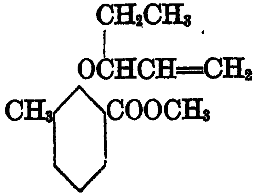


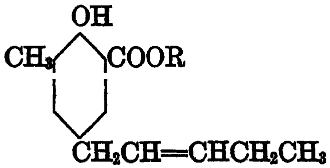
XXVIII

structure XXVII was obtained by removal of the ester group by hydrolysis and decarboxylation, and oxidation of the resulting phenol as the aryloxyacetic acid derivative. The products were 3-methyl-4-hydroxybenzoic acid, as the aryloxyacetic acid derivative (XXVIII), and benzoic acid, showing that there was a cinnamyl side chain in XXVII. A similar result was obtained with the γ-methylallyl ether of the same phenol; rearrangement was not accompanied by inversion.

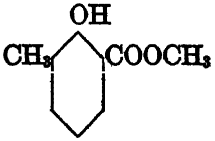
Mumm and coworkers (89) studied a pair of isomeric ethers, γ-ethylallyl 2-carbomethoxy-6-methylphenyl ether (XXIX) and the corresponding α-ethylallyl ether (XXX). It is probable that each of the ethers contained an appreciable amount of the other, because of the difficulty of obtaining

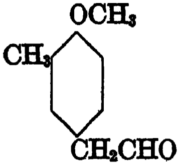

XXIX
γ-Ethylallyl 2-carbomethoxy-6-methylphenyl ether


XXX
α-Ethylallyl 2-carbomethoxy-6-methylphenyl ether


XXXI

the isomeric 1-chloro-2-pentene and 3-chloro-1-pentene pure (57, 77), but the two ethers differed enough in their chemical behavior to show that they were actually different compounds. Both on heating in diethylaniline gave the same product XXXI (R equals CH_3), together with appreciable amounts of *o*-cresotic ester (XXXII), the identity of the two samples of rearrangement product obtained being proved by a mixed melting point of the acid (XXXI; R equals H) obtained from them by hydrolysis.


XXXII
Methyl *o*-cresotate

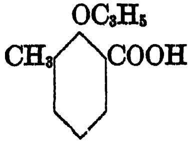

XXXIII

The α-ethylallyl ether (XXX) rearranged during hydrolysis with alcoholic alkali to XXXI (R equals H), but the isomeric ether (XXXIX) did not rearrange under the same conditions; both ethers were cleaved to *o*-cresotic ester by one mole of hydrogen with palladium catalyst.

The structure of the rearrangement product (XXXI) was proved by decarboxylation, methylation, and ozonization to the aldehyde XXXIII, which was analyzed as the semicarbazone. From this work it appears that inversion takes place in the para rearrangement when an α-substituted allyl ether is rearranged, and that there is no evidence for the anomalous rearrangement in the para series. The difference in ease of rearrangement of the two ethers is striking; the α-substituted ether rearranges on standing for some time, as well as in alcoholic alkali,—conditions under which the γ-substituted ether is unaffected.

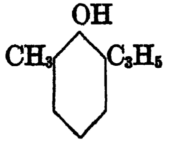
E. REARRANGEMENT OF ALLYL ARYL ETHERS INVOLVING THE DISPLACEMENT OF CARBOXYL AND ALDEHYDE GROUPS

One aspect of the rearrangement which has not been studied since Claisen's pioneer work is the reaction in which a carboxyl or aldehyde group in the ortho- or para-position is displaced from the molecule by the migrating allyl group. The allyl ether of *o*-cresotic acid (I) is an example; it starts to evolve carbon dioxide at 100°C., and gives a mixture of 80 per cent of the displacement product (II) and 20 per cent of the para-product (III) (25, page 83). If the para-position is blocked, the reaction gives practically quantitative yields; with the allyl ether of diallylsalicylic acid (IV) (25, page 79) evolution of carbon dioxide starts at 100°C. and a quantitative yield of 2,4,6-triallylphenol is obtained. The reaction goes just as well with the dichloro compound corresponding to IV.

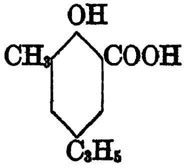


I

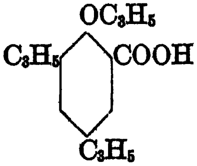
Allyl ether of *o*-cresotic acid



II

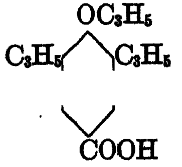


III

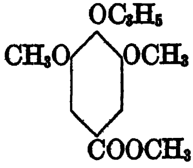


IV

Allyl ether of diallylsalicylic acid



V



VI

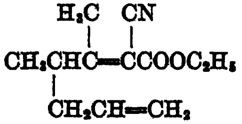
Allyl 2,6-dimethoxy-4-carbomethoxyphenyl ether

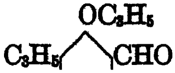
A carboxyl group in the para-position is eliminated with equal facility. Compound V (25, page 90) evolves 99 per cent of the theoretical amount of carbon dioxide, the evolution starting at 150°C. A particularly interesting example is allyl 2,6-dimethoxy-4-carbomethoxyphenyl ether (VI) (44), which is hydrolyzed and rearranged with loss of the carboxyl group by refluxing with aqueous alkali for 10 hr.; the product, 2,6-dimethoxy-4-allylphenol, is obtained in 95 per cent yield.

The displacement reaction with aldehyde derivatives is entirely analogous, although a slightly higher temperature seems to be necessary to evolve carbon monoxide. The allyl ether of allylsalicylaldehyde (VII) starts to give off carbon monoxide at 180°C. and gives 72 per cent of the theoretical amount, yielding a mixture of the displacement product (VIII) and the para product (IX) in the ratio of three to one (25, page 102).

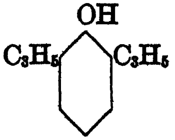
TABLE 4

Rearrangement involving elements other than carbon and oxygen

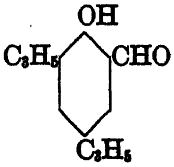
		REFERENCES
Allyl *N*-phenylbenzimino ether.	*N*-Allylbenzanilide	(90)
α-Methylallyl *N*-phenylbenzimino ether....................	*N*-(γ-Methylallyl)benzanilide	(90)
γ-Methylallyl *N*-phenylbenzimino ether....................	*N*-(α-Methylallyl)benzanilide	(90)
2-Allyloxyquinoline.............	*N*-Allyl-2-quinolone	(109)
2,6-Diallyloxy-7-methylpurine..........................	1,3-Diallyl-7-methylxanthine	(16)
2,6-Di-(α,γ-ethylmethylallyloxy)-7-methylpurine..........	1,3-Di-(α,γ-methylethylallyl)-7-methylxanthine	(16)
Allyl phenyl sulfide............	$1,2\text{-}C_6H_4(SH)(CH_2CH{=}CH_2)$	(51)
Allyl 4-methylphenyl sulfide....	$1,2,4\text{-}C_6H_3(SH)(CH_2CH{=}CH_2)(CH_3)$	(51)
Allyl thiocyanate..............	Allyl isothiocyanate	(17)
Cinnamyl thiocyanate..........	Cinnamyl isothiocyanate	(12)
γ-Methylallyl thiocyanate......	α-Methylallyl isothiocyanate	(90a)
α-Ethylallyl thiocyanate.......	γ-Ethylallyl isothiocyanate (?)	(90a)
γ-Ethylallyl thiocyanate.......	α-Ethylallyl isothiocyanate (?)	(90a)
Ethyl (1-methylpropenyl)allylcyanoacetate.................	 $CH_3\underset{\displaystyle CH_2CH{=}CH_2}{\underset{\vert}{C}}H\overset{\displaystyle H_3C}{\overset{\vert}{C}}{=}\overset{\displaystyle CN}{\overset{\vert}{C}}COOC_2H_5$	(31)



VII
Allyl ether of
allylsalicylaldehyde

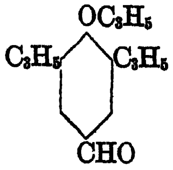


VIII



IX

The allyl ether of 3,5-diallyl-4-hydroxybenzaldehyde (X) starts to lose carbon monoxide at 170°C., giving 74 per cent of the theoretical amount,



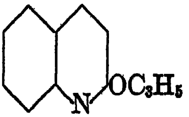
X

Allyl ether of 3,5-diallyl-4-hydroxybenzaldehyde

and gives a 51 per cent yield of 2,4,6-triallylphenol (25, page 108).

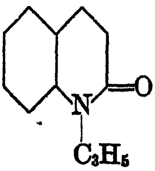
F. REARRANGEMENT OF COMPOUNDS STRUCTURALLY ANALOGOUS TO THE ALLYL ARYL ETHERS

Several classes of allyl ethers are known in which the grouping C═C—C—O—C═N is involved. The first example was reported by Tschitschibabin and Jeletzsky (109), who found that 2-allyloxyquinoline (I) rearranged to *N*-allyl-2-quinolone (II) on distillation at 325°C. Bergmann and Heimhold (16) reported a similar migration from oxygen to nitrogen with 2,6-allyloxy-7-methylpurine (III), and, from a study of the α-methyl-γ-ethylallyl derivative, concluded that rearrangement was accompanied by inversion.



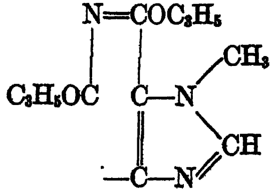
I

2-Allyloxyquinoline



II

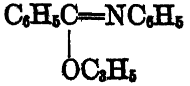
N-Allyl-2-quinolone



III

2,6-Allyloxy-7-methylpurine

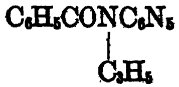
Mumm and Möller (90) showed that allyl *N*-phenylbenzimino ether (IV) rearranged quantitatively in 3 hr. at 210–215°C. to *N*-allylbenzanilide (V). Rearrangement of the γ-methyl-substituted ether (VI) gave inversion,



$$\begin{array}{l}C_6H_5C{=}NC_6H_5\\ \quad\ \ |\\ \quad OC_3H_5\end{array}$$

IV

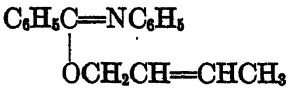
Allyl *N*-phenylbenzimino ether



$$\begin{array}{l}C_6H_5CONC_6N_5\\ \qquad\quad\ |\\ \qquad\ \ C_3H_5\end{array}$$

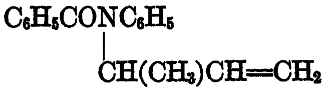
V

N-Allylbenzanilide



$$\begin{array}{l} C_6H_5C{=}NC_6H_5 \\ \quad | \\ \quad OCH_2CH{=}CHCH_3 \end{array}$$

VI



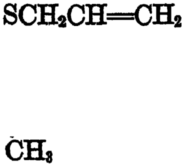
$$\begin{array}{l} C_6H_5CONC_6H_5 \\ \qquad\quad | \\ \qquad\quad CH(CH_3)CH{=}CH_2 \end{array}$$

VII

N-(α-Methylallyl)benzanilide

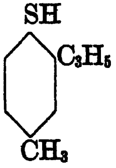
yielding *N*-(α-methylallyl)benzanilide (VII), whose structure was proved by catalytic hydrogenation and hydrolysis to *sec*-butylaniline. The α-methylallyl ether, isomeric with VI, also gave inversion, yielding *N*-(γ-methylallyl)benzanilide. The system C═C—C—O—C═N is thus similar to that in the allyl aryl ethers in its behavior.

Hurd and Greengard (51) have shown that allyl phenyl sulfides, containing the system C═C—C—S—C═C, give a rearrangement similar to that of their oxygen analogs, although it goes much more slowly. Thus, allyl 4-methylphenyl sulfide (VIII) on refluxing for 4 hr. at 228–264°C. gives a 27 per cent yield of the rearrangement product IX, and 45 per cent



VIII

Allyl 4-methylphenyl sulfide

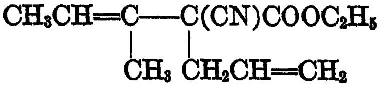


IX

of the starting material is recovered unchanged. The analogous oxygen ether rearranges much more rapidly (*cf.* page 15).

The system C═C—C—S—C≡N is contained in allyl thiocyanate, which, as is well known, rearranges very rapidly on distillation to allyl isothiocyanate, $CH_2{=}CHCH_2NCS$ (17). Even methyl thiocyanate, CH_3SCN, reacts similarly on heating at 180°C. (47), so that the system R—S—C≡N is very much more mobile than R—O—C═C. Bergmann (12) has shown that in the rearrangement of cinnamyl thiocyanate, $C_6H_5CH{=}CHCH_2SCN$, there is no inversion, the product being $C_6H_5CH{=}CHCH_2NCS$. Mumm and Richter (90a) have found, however, that γ-methylallyl thiocyanate, $CH_3CH{=}CHCH_2SCN$, rearranges with inversion to give α-methylallyl isothiocyanate, $CH_2{=}CHCH(CH_3)NCS$.

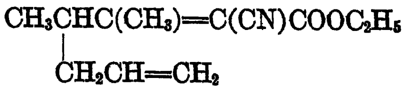
A very interesting rearrangement involving the carbon system $C{=}C{-}C{-}\overset{*}{C}{-}C{=}C$ (the carbon corresponding to the ether oxygen is starred) has been reported recently by Cope and Hardy (31). Ethyl (1-methylpropenyl)allylcyanoacetate (X), when heated for 4 hr. at 150–160°C. or for 20 min. at 260°C., rearranged completely to XI, the



$$\begin{array}{l} CH_3CH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}\underset{\displaystyle CH_2CH{=}CH_2}{\underset{|}{C}}(CN)COOC_2H_5 \end{array}$$

X

Ethyl (1-methylpropenyl)-
allylcyanoacetate



$$CH_3\underset{\displaystyle CH_2CH{=}CH_2}{\underset{|}{C}H}C(CH_3){=}C(CN)COOC_2H_5$$

XI

reaction involving a shift of the allyl group to the γ-carbon in the chain, and a shift of the double bond to a position of conjugation with the cyano and carbethoxyl groups. The esters with saturated alkyl groups instead of the allyl group do not rearrange.

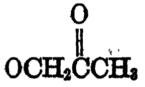
In all of the other rearrangements of the Claisen type, the key atom is either oxygen or sulfur, which have unshared pairs of electrons to participate in or initiate electronic shifts; in this case the carbon has no unshared pairs and the rearrangement must be ascribed to the tendency of X to go into the much more stable conjugated form (XI).

The allylanilines, which contain the system C═C—C—N—C═C, have been studied by Carnahan and Hurd (20). *N*-Allylaniline gives a small amount of aniline when heated at 275°C. for 12 hr., and at higher temperatures propene is evolved; *N*,*N*-diallylaniline gives propene, aniline, and *N*-allylaniline. *N*-Allylacetanilide and *N*-allyltosylanilide give only complex decomposition products.

The grouping N≡C—C—O—C═C is present in phenoxyacetonitrile (XII), but the compound is stable toward long refluxing; the corresponding

OCH_2CN

XII
Phenoxyacetonitrile



$$OCH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_3$$

XIII

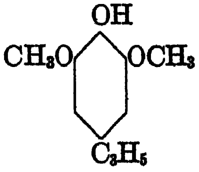
derivative of *p*-cresol is less stable but no rearrangement product is isolated (94). *p*-Cresoxyacetone, which contains the system O═C—C—O—C═C, gives no rearrangement product on refluxing (106).

From the foregoing work and from section A it appears that the system present in the allyl ethers, C═C—C—O—C═C, can be altered by substitution of certain other elements in the —O—C═C part, but that any change in the skeleton of the allyl part, either by substitution of other elements or by changing the position of the double bond, makes rearrangement impossible.

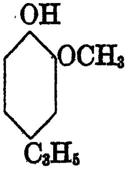
III. Applications of the Claisen Rearrangement

A. APPLICATIONS IN SYNTHETIC WORK

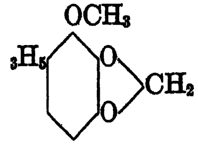
The Claisen rearrangement is a useful reaction in synthetic work, because it provides an easy way of introducing allyl groups into a wide variety of phenolic compounds. Many naturally occurring allylphenols have been synthesized by this method, such as elemicin (I) (83, 44), eugenol (II) (21, page 118), croweacin (III) (7), and dill apiole (IV) (4). Fieser, Campbell, and Fry have used the Claisen rearrangement recently (37) to obtain diallylnaphthoquinones as model substances for vitamin K studies. The substituted allyl side chains occurring in natural compounds, such as farnesyl and phytyl, cannot be introduced by the Claisen rearrangement, because inversion gives a branched chain.[1]



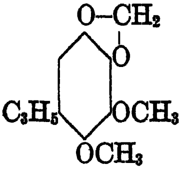
I
Elemicin



II
Eugenol



III
Croweacin



IV
Dill apiole

The allylphenols are also useful as intermediates, since they can be transformed into several other classes of compounds. The allyl side chain can, of course, be reduced catalytically, giving propylphenols; Bartz, Miller, and Adams (10) prepared a series of isobutylphenols for bactericidal tests by the rearrangement and reduction of substituted β-methylallyl phenyl ethers.

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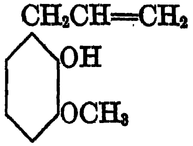
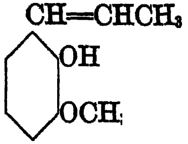
[1] Very recently Makino and Morii (111) have reported in a preliminary note that the difarnesyl ether of 1,4-naphthohydroquinone rearranges to give 2,3-difarnesyl-1,4-naphthohydroquinone (isolated as the diacetate). The structure of the rearrangement product was not proved, so that this work cannot be considered to conflict with the statement on page 518 that substituted allyl ethers after rearrangement are never attached by the same carbon which was attached to oxygen.

On heating with concentrated aqueous alkali, the allyl group in allylphenols is isomerized to a propenyl group; thus 2-methoxy-6-allylphenol (V) is isomerized to the propenyl compound (VI) by heating one part of V with two parts of powdered potassium hydroxide and one of water for 1 hr. at 170°C. (25, page 52). This isomerization of the allyl group never seems to take place under the conditions of the rearrangement of the allyl aryl ethers. Propenyl compounds are oxidized by mercuric acetate, and allyl compounds are not, hence this is a useful test reagent for distinguishing allyl- and propenyl-phenols (9); γ,γ-dialkylallyl compounds, however, are oxidized by it (24), so that it must be applied with caution in such cases.

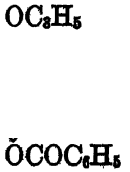


V
2-Methoxy-6-allylphenol

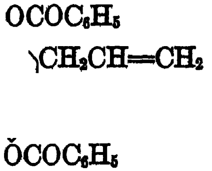


VI
2-Methoxy-6-propenylphenol

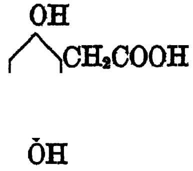
The allylphenols can be oxidized, and in certain cases this is a useful method of preparing substituted phenylacetaldehydes (44, 98, 85) or phenylacetic acids. For example, homogentisic acid (IX), otherwise obtained only with great difficulty, can be made from hydroquinone in 26 per cent yield by rearrangement of the benzoate of hydroquinone monoallyl ether (VII), followed by ozonolysis (as the dibenzoate, VIII) and hydrolysis to IX (43). The propenylphenols obtained by isomerization can also be ozonized to hydroxyaldehydes (67, 85), but these can usually be obtained more readily by other methods.



VII
Benzoate of hydroquinone
allyl ether

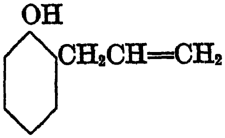


VIII

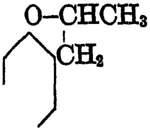


IX
Homogentisic acid

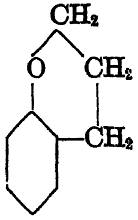
When heated with acid catalysts, such as pyridine hydrochloride (25, page 26), hydrobromic acid–acetic acid, or formic acid (30), *o*-allylphenols are isomerized to 2-methyldihydrobenzofurans (X → XI). By treating the acetate of the allylphenol with hydrogen bromide and a peroxide, the



X
o-Allylphenol

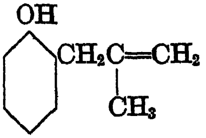


XI

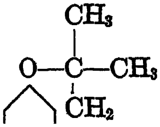


XII

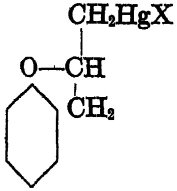
isomeric chroman (XII) can be obtained (53). The dihydrobenzofuran is frequently found as a by-product in the Claisen rearrangement and is evidently formed by isomerization of the *o*-allylphenol by heat (10); the tendency for ring closure is increased by alkyl groups on the double bond. Thus Bartz, Miller, and Adams (10) found that 2-(β-methylallyl)phenol (XIII) isomerized to the dihydrobenzofuran (XIV) on heating or even on standing with anhydrous magnesium sulfate in petroleum ether solution.



XIII
2-(β-Methylallyl)phenol



XIV



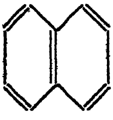
XV

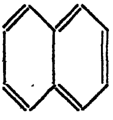
Treatment of *o*-allylphenols with mercuric salts gives derivatives of mercuridihydrobenzofurans of type XV (86). Bromination of *o*-allylphenols gives a mixture of bromomethyldihydrobenzofurans (1).

B. DETERMINATION OF BOND STRUCTURES IN AROMATIC COMPOUNDS

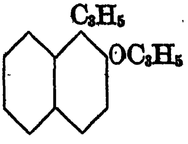
It is obvious (section A) that the ether oxygen of an allyl ether must be attached to a double bond for rearrangement to take place. This fact has been utilized by Fieser and coworkers to determine the bond structures of aromatic compounds.

As an example naphthalene may be cited (38). Two Kekulé structures may be written for naphthalene and its derivatives, I and II; if it is possible to obtain reaction products derived from structure II, a substituted allyl



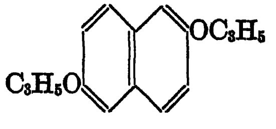


II



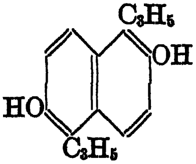
III

naphthyl ether such as III should rearrange by means of the 2,3-double bond, to give 1,3-diallyl-2-naphthol. Actually, as Claisen (23) showed, III is unchanged by long heating, and hence must be unable to react as structure II. Similarly, 2,6-diallyloxynaphthalene (IV) rearranges to V in 85 per cent yield on heating to 190°C. for a few minutes, but the diether (VI) from V does not rearrange in 5 min. at 200°C., and decomposes on longer heating, giving no alkali-soluble material (38). These facts indicate that naphthalene derivatives react as if they had double bonds in the 1,2- and 5,6-positions, and no double bonds in the 2,3- and 6,7-positions; the reactions show that the symmetrical formula (I) is satisfactory for expressing the chemical behavior of naphthalene compounds. This is usually expressed by saying that the double bonds are fixed.

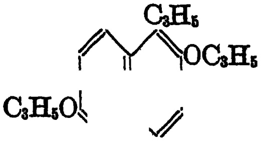


IV

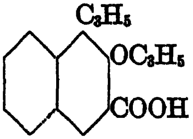
2,6-Diallyloxynaphthalene



V



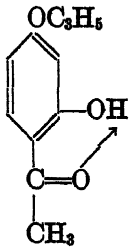
It would be interesting to see whether the compound VII would give the displacement reaction to form 1,3-diallyl-2-naphthol, since the displacement reaction goes at much lower temperatures than the ordinary rearrangement.

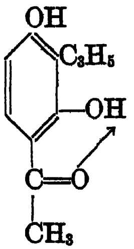


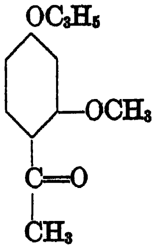
VII

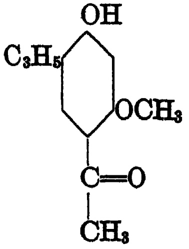
Several aromatic hydrocarbons have been studied by the Claisen rearrangement to determine the bond structures, among them naphthalene (38, 13), anthracene (39), phenanthrene (40), hydrindene (79), fluorene (78), and other compounds, such as chromone (96), flavone (96), and fluorenone (14).

An interesting application of the Claisen rearrangement showing the effect of chelation on the fixation of bonds in benzene derivatives has been developed by Baker and Lothian (5,6). Several lines of evidence indicate that a chelate ring, such as that in VIII, contains a double bond; that this arrangement of the bonds actually determines the reactions of the compound is shown by the formation of IX in 85 per cent yield by rearranging VIII at 210°C. If instead of VIII, its methyl ether X, which cannot form


VIII


IX


X


XI

a chelate ring, is rearranged, the allyl group migrates to the other free ortho-position, giving XI. The latter is the usual position for substitution in resorcinol compounds, but the stability of the chelate ring in VIII is such that fixation of the double bonds occurs, and the tendency for formation of the symmetrical product XI is overcome.

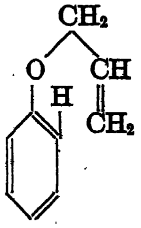
Similar reactions are observed with compounds analogous to VIII and IX, but having aldehyde and propionyl groups instead of acetyl groups.

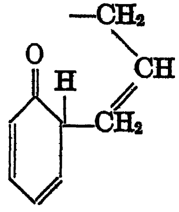
IV. The Mechanism of the Rearrangement

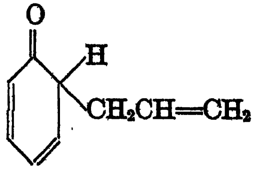
A. MECHANISM OF THE REARRANGEMENT TO THE ORTHO-POSITION

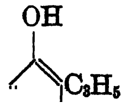
In addition to the facts mentioned so far, any mechanism for the rearrangement must be in harmony with the kinetics of the reaction. Kincaid and Tarbell (70), in a study of the rearrangement of allyl 4-methylphenyl ether, found that the reaction was strictly first order over a fivefold change of concentration in diphenyl ether solution, and that the initial rate in the pure liquid was the same as the rate in solution. The rate of reaction was not appreciably affected by adding 10 per cent of dimethylaniline or 1 per cent of acetic acid, and therefore the rearrangement does not go by a mechanism which requires catalysis by acids or bases. These results support the conclusion of Hurd and Schmerling (59), from experiments on mixtures, that the rearrangement is intramolecular.

In the paper reporting the first instance of inversion, Claisen and Tietze (29) suggested the first mechanism for the rearrangement. Their idea was that the γ-carbon atom of the allyl group came into close contact with


I

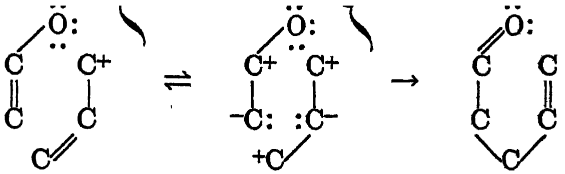

II


III



the ortho-carbon atom of the nucleus (I); the carbon–oxygen bond broke, the aromatic nucleus assumed the *o*-quinonoid form (II), and simultaneously the allyl group attached itself to the nucleus by the free bond, the double bond in the allyl group shifting. These processes, all occurring practically simultaneously, gave III, which immediately enolized to give IV.

This mechanism is primarily a description of the rearrangement, and is a satisfactory picture. Later writers have restated Claisen's description in electronic terms (90, 89, 33), the clearest account being given by Hurd and Pollack (57). According to them, the system C═C—C—O—C═C goes through the changes indicated below; the carbon–oxygen link is



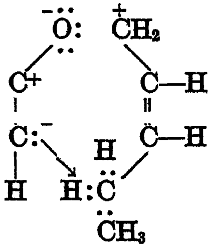
V VI VII

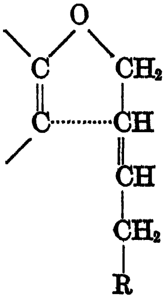
broken, with the pair of electrons going to the oxygen, while the allyl group undergoes a redistribution of electrons and attaches itself to the nucleus by the γ-carbon atom. The last step is the enolization to the phenolic form. It would be expected that there would be considerable resonance energy in the activated complex VI, which would reduce the energy necessary to break the carbon–oxygen bond and therefore the activation energy necessary for the reaction.

This cylic mechanism agrees with most of the facts known about the simple rearrangement. The first-order reaction kinetics are consistent with the idea that the rate-determining step is the change of VI to VII, and the subsequent enolization of VII must take place very rapidly, since the rate of rearrangement is not affected by dimethylaniline. The invariable occurrence of inversion in the ortho rearrangement is a necessary result of the cyclic form of the activated complex. The displacement of carbon dioxide by the allyl group in allyl 2-carboxyphenyl ethers (page 529) can be correlated with the ease of decarboxylation of β-keto acids by assuming the existence during rearrangement of a β-keto acid analogous to III, which undergoes decarboxylation immediately (21, page 74). This idea is not very satisfactory for explaining the displacement of carbon monoxide from allyloxy aldehydes, however, since β-keto aldehydes do not lose carbon monoxide readily (27).

The failure of the allylanilines to rearrange may be due to the fact that nitrogen has a smaller tendency than oxygen to become a negative ion, and the process of partial ionization cannot take place. On this basis one would expect that allyl phenyl sulfides should rearrange more rapidly than the oxygen compounds, since sulfur is more negative than oxygen, but it is reported that they rearrange much more slowly (51). The failure of propargyl ethers, such as $C_6H_5OCH_2C{\equiv}CH$, to rearrange may be caused by the fact that the $—C—C{\equiv}C$ group must be linear and hence cannot form the cyclic activated complex. The same would be true of $C_6H_5OCH_2C{\equiv}N$.

The mechanism given above fails to explain the course of the anomalous rearrangement in which the migrating group is attached by some carbon other than the γ-carbon. Hurd and Pollack (57) suggested that the γ-ethylallyl phenyl ether is probably a mixture of *cis*- and *trans*-forms, and that in the *cis*-form the δ-carbon is near the ortho-carbon; the activated complex would then be a seven-membered ring (VIII), which by a shift of two hydrogens and formation of a carbon–carbon bond would give the observed product. This extension of the cyclic mechanism has two drawbacks: (*1*) If extended to the γ-propylallyl ethers, it requires an eight-membered ring analogous to VIII in the activated complex, which is sterically very unlikely. The formation of such a complex would take place so infrequently in comparison to the formation of the normal complex of type VI that only the normal product would be found, instead of a mixture. (*2*) A complex of type VIII would lack the stabilization by

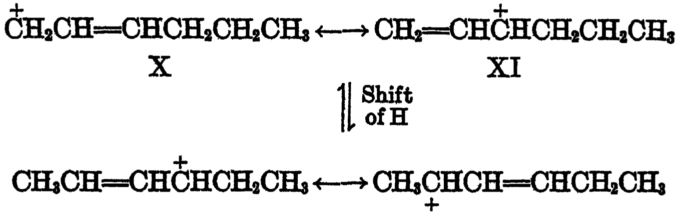

VIII


IX

resonance which is present in VI, and the activation energy for a reaction going through VIII would be much greater than for one going through VI.

The anomalous rearrangement can be explained formally by an activated complex (IX) in which the β-carbon atom is concerned in the bond formation with the ortho-carbon. This structure also would have less resonance energy than VI and would require a shift of two hydrogens and of the double bond to give the products obtained.

The anomalous rearrangement has been attributed to a dissociation process in which the substituted allyl group splits off as an ion or radical, which might then undergo the following processes (89):



$$\overset{+}{C}H_2CH{=}CHCH_2CH_2CH_3 \longleftrightarrow CH_2{=}CH\overset{+}{C}HCH_2CH_2CH_3$$

X XI

$$\Big\Updownarrow \text{ Shift of H}$$

$$CH_3CH{=}CH\overset{+}{C}HCH_2CH_3 \longleftrightarrow CH_3\underset{+}{C}HCH{=}CHCH_2CH_3$$

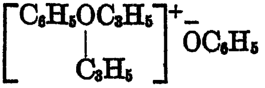
XII XIII

The observed products are derived from XI and XIII, and no products are found corresponding to the other resonance forms, X and XII.

In the migration of the ethylallyl group to the para-position, only the compound derived from X is formed from both α-ethylallyl and the γ-ethylallyl ethers (page 527). The para rearrangement certainly involves a dissociation (section B), and if the ortho rearrangement went by a dissociation process also, the ethylallyl group should isomerize to the same structure in both cases while in the ion or radical form. That the ethylallyl group gives products derived from XI and XIII in the ortho rearrangement, and from X in the para, is a serious objection against the dissociation mechanism for the ortho rearrangement.

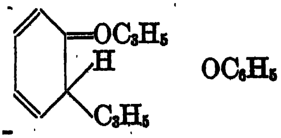
It is certainly significant, in considering the mechanism of the anomalous rearrangement, that α-substituted allyl ethers, such as $ArOCH(CH_2CH_3)CH{=}CH_2$ give only the normal product. This may be due to the fact that the carbon–oxygen bond in these ethers is much more readily broken than that in the γ-substituted compounds. It is well known that secondary ethers are much more readily cleaved by acids than primary ethers (82), and the α-substituent in the allyl ethers may favor the formation of the activated complex VI by promoting electron displacements toward the oxygen. The rearrangement would thus take place at a lower temperature than that of the γ-substituted ethers, and the complicated changes which result in the anomalous products in the latter case would be avoided. The evidence, which is scanty, indicates that α-substituted allyl ethers do rearrange more rapidly than the γ-substituted compounds (102, 89).

The oxonium mechanism of Niederl and Storch (92; *cf.* 57), which was suggested to explain the rearrangements of alkyl phenyl ethers by acidic catalysts and extended to include the Claisen rearrangement, postulates formation of an oxonium salt (XIV). This salt then rearranges through an



$$\left[\begin{matrix}C_6H_5OC_3H_5\\ |\\ C_3H_5\end{matrix}\right]^{+}\bar{O}C_6H_5$$

XIV



XV

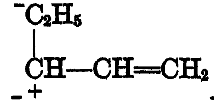
o-quinonoid structure (XV), which breaks up to give the *o*-allylphenol and one molecule of ether. Hurd and Pollack (57) have pointed out two serious arguments against this theory: it does not explain inversion, and it predicts the formation of some allyl 2-allylphenyl ether by decomposition of XV to yield this product and phenol. This is not observed. The mechanism would also require second-order kinetics, which are not found, and the addition of a base like dimethylaniline to the reaction mixture should stop rearrangement completely, since the allyl phenyl ether would form an ammonium salt with the dimethylaniline in preference to an oxonium salt with the very weakly basic ether. Actually, the rate is unaffected by adding as much as 10 per cent of dimethylaniline.

From this discussion, it is evident that no single scheme is compatible with all of the facts known about the rearrangement to the ortho-position; the cyclic mechanism is the most satisfactory, but is reconciled with difficulty with the anomalous rearrangement. The dissociation mechanism is entirely unsatisfactory.

B. MECHANISM OF THE REARRANGEMENT TO THE PARA-POSITION

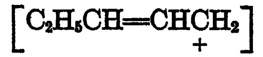
The kinetics of the rearrangement to the para-position are very similar to those for the ortho-position (107); the reaction is first order both in solution and in the pure liquid, and the rate is not affected markedly by dimethylaniline or acetic acid, although the para rearrangement must involve a dissociation of the allyl group, either as an ion or radical, followed by a substitution reaction in the para-position. This follows both from consideration of the spatial factors and from the fact that inversion in the para rearrangement is the exception. Inspection of models shows that the formation of a cylic intermediate is very improbable, because the distances are too great and because of the distortion of the bond angles of the atoms which would be required (107).

Mumm's work on the para rearrangement of α- and γ-substituted allyl ethers (page 527) is further strong support for the idea that para rearrangement involves dissociation. The α-ethylallyl group



$$\overset{\overline{\ }C_2H_5}{\underset{-+}{\overset{|}{C}H}}{-}CH{=}CH_2$$

after dissociation isomerizes to the form



$$\left[C_2H_5CH{=}CH\underset{+}{C}H_2\right]$$

before attaching itself to the para-position; the γ-ethylallyl group, being already in this form, which is evidently the more stable of the two, gives the same rearrangement product. The fact that the two isomeric ethers give the same product is evidence that they pass through a common intermediate state.

The allyl group obviously may dissociate as a positive ion or as a free radical; serious objections can be raised to both. Against the ionic intermediate is the observation of Mumm (89) that rearrangement can take place on heating in alcoholic alkali; if a positive allyl ion were present, it should combine with an hydroxyl ion to give allyl alcohol.

If radicals were the intermediate stage, one would expect that they would react with the solvent or dimerize to an appreciable extent, so that lower yields of rearrangement product would be obtained. Thus Hickinbottom (45) finds that benzyl phenyl ether heated in quinoline at 250°C. gives benzylquinolines, hydroxyphenylquinolines, and toluene, which indicates that dissociation of the ether into radicals occurs. There is no evidence for the formation of similar products from the Claisen rearrangement.

Hurd and Pollack (57) have suggested that rearrangement to the para-position goes by two steps,—first a shift of the allyl group with inversion to the ortho-position, as described for the ortho rearrangement, followed by another shift with inversion to the para-position. The two inversions would give the result of no inversion, which is contrary to the results of Mumm mentioned above. It seems likely, however, that, as this mechanism suggests, the dissociated allyl group, whether ion or radical, does not get out of the sphere of influence of the other fragment and that recombination of the two takes place more rapidly than other possible reactions.

It is clear that no single mechanism can explain all of the facts observed in the rearrangement of allyl ethers, and that there are many phases of the process that are imperfectly understood.

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Because of the unusual length of two of Claisen's papers (21, 25), they are quoted with the page number of the reference following the reference number.

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THE ELECTRONIC THEORY OF ACIDS AND BASES

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CONTENTS

I. FOREWORD

A. Introduction

From the beginning of the history of chemistry the question as to the nature of acids and bases has been one of great interest. The answer to the question has been revised many times and is at present the subject of considerable controversy.

None of the three current theories of acids and bases satisfactorily explains more than a portion of their experimental behavior. For forty years an increasing amount of data has compelled realization of the fact that acid-base phenomena are far more widespread than is generally acknowledged. Those who have grasped this fact have already abandoned the hydrogen ion-hydroxyl ion theory. Yet neither of the two alternatives is inclusive enough to cover all the data.

The theory of solvent systems conforms to the experimental fact that there are many other substances besides those containing hydrogen which exhibit typical acid properties. But it goes astray in making the definitions of acid and base as rigidly dependent upon the solvent as does the hydrogen ion-hydroxyl ion theory.

The proton theory emphasizes the important fact that acid–base phenomena can be observed in any solvent or even in the absence of a solvent. It also takes into account the experimental fact that there are many other substances besides the hydroxyl ion which exhibit typical basic properties. Yet it does not recognize the complementary data with regard to acids. The followers of Brönsted have maintained that only substances capable of giving up protons can be called acids.

We have, then, two independent and, in important features, contradictory theories of acids and bases. This situation seems to be due to the neglect of two factors very important in contemporary chemistry: first, a portion of the experimental data, and second, the electronic theory of the covalent bond. Probably such neglect was natural and even necessary in the early stages of the development of each theory. Possibly neither would have accomplished as much as it has without some such limitation. However, as a result of this neglect, neither theory gives us much of an insight into the fundamental nature of acids and bases.

The most powerful theoretical tool now available to the chemist is undoubtedly the electronic theory of valency, which we owe to the brilliant intuition of G. N. Lewis (76, 77). It has been used with remarkable results by workers in many fields, yet the only one who has applied it systematically to the problem of the nature of acids and bases has been Lewis himself (77 to 81). When the theory had so well demonstrated its widespread usefulness, one might expect that an attempt by its author to apply it to acids and bases would meet with a favorable reception. But this attempt has been ignored where it has not been actively opposed. Walden has been almost bitter in his ridicule of the ideas of Lewis (102), but he reveals, by his misinterpretations of their consequences, that he has not understood them. Walden's opposition must have had considerable influence in preventing serious consideration of the proposals of Lewis. Yet Lewis' application of his theory to acids and bases explains their properties in the fundamental terms of a simple inherent difference in the electronic structure of the molecules themselves. It also takes into account both portions of the data neglected by the other two theories.

From an experimental standpoint it seems that a substance which exhibits the properties of an acid should be called an acid, regardless of preconceived notions about the dependence of acid properties on some particular element. Those properties have been agreed upon from the beginning. Yet many substances possessing them are not now recognized by most chemists as acids. This situation persists in spite of the fact that some of these substances were once called acids,—when the principal criterion of an acid was its experimental behavior.

In this paper the emphasis is upon experimental behavior. Substances which possess the properties of acids are properly called acids; substances having the properties of bases are properly called bases.

B. *Historical development of acid-base theory*

Some of the properties by which acids were recognized when the term first came into use were listed by Boyle (102) as follows: they dissolve many substances; they precipitate sulfur from its solution in alkalies; they change blue plant dyes to red; they lose all these properties on contact with alkalies. These were recognized as the properties of aqueous solutions of acids. If the solution of a substance in water had these and other typical acid properties, the substance itself was known as an acid. Thus the gases carbon dioxide and sulfur trioxide were called acids because their solutions exhibited the properties common to all aqueous solutions of acids.

This strictly experimental approach was largely abandoned during the series of controversies which began with Lavoisier's attempt to make oxygen the necessary constituent of all acids. After Davy had shown that some acids do not contain oxygen and that many oxides are not acids, hydrogen became the "acidifying principle." Davy himself wrote in 1814 "that acidity does not depend upon any particular elementary substance, but upon peculiar arrangement of various substances" (38). We shall see how nearly correct Davy was. But Liebig successfully maintained the hydrogen theory against Berzelius by defining an acid as any substance which contained easily replaceable hydrogen atoms.

With the advent of the Arrhenius theory of ionization, an acid was defined as a hydrogen compound ionizing in water solution to give hydrogen ions. A base was a hydroxyl compound which would give hydroxyl ions in water solution. These definitions became quite general, in spite of the efforts of several investigators to show how absurd they were. The exaggeration of the importance of ions in chemical reactions was at its height. A physical chemistry text of the period, as quoted by Folin and Flanders (20), contained the statement that "We have already reached a point where we can say that nearly all, if not all, chemical reactions are due to ions, molecules as such not entering into chemical action." Such an atmosphere was not conducive to a scientific approach, and the work of Collie and Tickle (10), Hantzsch (43, 44), Folin and Flanders (21), and Lapworth (72) was largely ignored.

Collie and Tickle (10), in their paper published in 1899, suggest that oxonium salts are similar to ammonium salts. They refer to "such bases as those of the pyridine series" and even mention a "hypothetical base oxonium hydroxide, OH_3OH". Hantzsch (43, 44) noted the basic action of water, methyl alcohol, and dimethyl ether in anhydrous sulfuric acid.

Folin and Flanders, in a paper published in 1912 (21), reported the titration of a large number of acids in such solvents as benzene, toluene, chloroform, and carbon tetrachloride. They used sodium ethylate and sodium amylate as bases and phenolphthalein as an indicator. They noted that weak acids which cannot be titrated in water give excellent results in organic solvents. Even hydrogen sulfide was titrated. They found their solutions of acids practically non-conducting and concluded that there were very few ions present. This has been supported by the work of Fuoss and Kraus (27, 28, 85). Carbon dioxide could not be titrated in either chloroform or benzene. As we shall see, this seems to agree with Lewis' statement that carbon dioxide is a "secondary" acid (78). The most striking thing about the paper appears in a footnote in which the authors mention that mercuric chloride can be titrated with phenolphthalein and sodium ethylate in the same manner as any other acid, but they failed to draw the logical conclusion that mercuric chloride might be an acid. Lapworth (72) was one of the first to attack the Arrhenius–Ostwald theory of the catalytic activity of acids. However, these and similar investigations failed to make an impression upon the followers of Arrhenius, until the concept of the covalent bond began to relegate ionic reactions to their proper importance in chemistry.

Meanwhile the development of the theory of solvent systems was begun by Franklin in 1905 (22 to 25). Reasoning from formal analogy to the hydrogen ion–hydroxyl ion theory he defined acids and bases in liquid ammonia. According to his theory, if water ionizes into hydronium (or oxonium) and hydroxyl ions, liquid ammonia must ionize into ammonium and amide ions. Substances like ammonium chloride are acids and substances like sodium amide are bases in liquid ammonia. Ammonia solutions of acids and bases neutralize each other just as aqueous solutions do. For example:

$$\begin{array}{cccc} OH_3Cl + & NaOH \rightarrow & NaCl + & 2H_2O \\ NH_4Cl + & NaNH_2 \rightarrow & NaCl + & 2NH_3 \\ \text{acid} & \text{base} & \text{salt} & \text{solvent} \end{array}$$

Other properties of acids and bases, such as the reaction of acids with metals and of bases with non-metals (4), were observed. The similarity between ammonia and water solutions was demonstrated very widely. Even acids like $B(OH)_3$ and $B(NH_2)_3$ were compared, and the latter was called an ammono acid. It appeared that the acid properties of both the hydronium and the ammonium ions must be due to the proton. The question then arose as to whether the idea of the solvent system could be applied to systems in which no protons were present.

Germann (29, 30, 31), Cady and Elsey (9), Jander (57 to 65), Wickert

(105), and Smith (100) have extended the solvent system theory of acids and bases to include aprotonic systems. Germann showed that aluminum chloride in phosgene has typical acid properties. The solution dissolves metals with evolution of carbon monoxide gas and is neutralized by metallic chlorides such as calcium chloride. Germann assumed that the aluminum chloride forms with the solvent a complex which he called a solvo acid. His definitions of acids and bases were formal and complicated, but were simplified by Cady and Elsey (9). They defined an acid as a solute which gives rise to a cation characteristic of the solvent and a base as a solute which gives rise to an anion characteristic of the solvent.

Jander and his coworkers used the same definitions to interpret the results of their work in sulfur dioxide (57 to 65, 104). Smith changed the definitions somewhat in reviewing the work with selenium oxychloride as a solvent (100, 107, 73, 74, 75, 66, 92). He defined an acid as an electron-pair acceptor toward the solvent, and a base as an electron-pair donor toward the solvent. These definitions, suggested in 1938, first show the influence of Lewis' proposals made in 1923 (77).

The extreme of formalism has been reached by Wickert in his definitions of acids and bases in terms of the solvent system (105, 90). He does not hesitate to overlook such experimental behavior as amphoterism in order to state his definitions wholly in terms of ions. Shatenstein also (97) has pointed out one of the several inconsistencies in Wickert's presentation. Wickert defines an acid as an ionic compound the cation of which has an incomplete electronic configuration. Yet he admits that ammonium salts are acids in ammonia. Another contradiction of the experimental facts occurs in that antimony trichloride is correctly listed as an acid, but aluminum chloride is not.

The essential ideas of the theory of solvent systems are summarized in table 1. In the first three examples, it is obvious enough that the acid which has reacted with each solvent is hydrogen bromide. Yet Smith seems to be the only adherent of the solvent system theory who recognizes that in examples 5 and 6 aluminum chloride and stannic chloride are true acids (100). And that is the beginning of the end of the theory.

The strength of the solvent system theory lies in its emphasis upon the fact that acid behavior is not confined to solutions containing proton-donors. The advocates of the theory have demonstrated that their acid solutions have all the typical experimental properties of aqueous solutions of hydrogen acids,—except the presence of the proton. The weaknesses of the theory are two: first, the attempt to limit acid-base phenomena to solvent systems, and second, the undue emphasis upon ionization as the most important factor in acid-base properties. Probably the first followed from the second. At any rate, many investigators have shown (10, 21, 39, 42, 43, 44, 50, 71, 72, 109) that ionization plays a far less important rôle than the followers of the solvent system theory would have us believe. It would appear that the theory merely describes one aspect of the nature of acids and bases: namely, their reactions with amphoteric solvents and the properties of the resulting solutions. We are most familiar with these properties, since they are most easily observed. A reluctance to go beyond them is readily understood, but for many chemists the Brönsted theory has overcome this reluctance, at least with respect to bases.

There are so many excellent discussions of the Brönsted theory (5, 7, 8, 35, 36, 37, 69, 84), that it is only necessary here to point out its one important weakness. The Brönsted theory admits of no acids other than proton-donors. As the proponents of the solvent system theory have shown, this does not correspond to the experimental facts. If the experimental approach is to prevail we cannot go on saying, as Meerwein (91), Shatenstein (97), and others do, that certain substances are "acid-analogous" in their properties, but are not acids simply because they do not contain hydrogen. Brönsted is undoubtedly correct in attributing acid–base properties to the molecules themselves rather than to their solutions. In this respect the Brönsted theory, as far as it goes, is closer to the experimental facts than the theory of the solvent system. Just as important is the conclusion that acids and bases are not necessarily ionic.

TABLE 1

Neutralization reactions according to the theory of solvent systems

NO.	SOLVENT	ACID +	BASE →	SALT +	SOLVENT
1	H_2O	H_3O^+, Br^-	K^+, OH^-	K^+, Br^-	$2H_2O$
2	NH_3	NH_4^+, Br^-	K^+, NH_2^-	K^+, Br^-	$2NH_3$
3	C_2H_5OH	$C_2H_5OH_2^+$, Br^-	K^+, $OC_2H_5^-$	K^+, Br^-	$2C_2H_5OH$
4	SO_2	SO^{++}, Br_2^-	K_2^+, SO_3^{--}	$2K^+$, Br^-	$2SO_2$
5	$COCl_2$	$COCl^+$, $AlCl_4^-$	K^+, Cl^-	K^+, $AlCl_4^-$	$COCl_2$
6	$SeOCl_2$	$(SeOCl)_2^+$, $SnCl_6^{--}$	$2K^+$, Cl^-	K_2^+, $SnCl_6^{--}$	$2SeOCl_2$
7	$SbCl_3$	Sb^{+++}, Br_3^-	$3K^+$, Cl^-	$3K^+$, Br^-	$SbCl_3$

Any attempt to reconcile the two contradictory theories of acids and bases must involve a deeper insight into their fundamental nature. Such an attempt has been made by Usanovich (101, 38) and by Lewis (77 to 81). Usanovich has defined an acid as any substance capable of giving up cations or of combining with anions, and a base as any substance capable of giving up anions or of combining with cations. He also suggests that oxidation–reduction reactions are a special case of acid–base phenomena. Acids combine with electrons as well as with anions, and bases give up electrons to acids. Oxidizing power is a limited phase of acidity, and both are due to attraction for negative particles. Some examples of neutralization according to Usanovich are given in table 2. Sulfur trioxide is an acid because it combines with the anion, O^{--}. Antimony pentasulfide is an acid because it combines with the sulfide ion. Ferric cyanide combines with the cyanide ion. Methyl iodide gives up the cation CH_3^+. Chlorine combines with two electrons from two sodium atoms. This theory is general and covers more of the experimental behavior (e.g., see 16), but objections may be raised to it.

Shatenstein (97) has called attention to certain inconsistencies in the above theory. Among these are the emphasis upon salt formation, and the formal reasoning involved in making ions so important in the scheme. In addition, one might mention the lack of correlation between the definitions and the degree of "coördination-unsaturation" which Usanovich recognizes is of great importance in determining acidity and basicity. Furthermore, the inclusion of oxidation–reduction as a special case of acid–base phenomena does not seem to be justified. The relationship is close, but, as we shall see, is not quite as Usanovich presents it.

TABLE 2

Neutralization reactions according to the theory of Usanovich

NO.	ACID +	BASE →	SALT
1	SO_3	Na_2O	Na_2SO_4
2	Sb_2S_5	$3(NH_4)_2S$	$2(NH_4)_3SbS_4$
3	$Fe(CN)_3$	$3KCN$	$K_3Fe(CN)_6$
4	CH_3I	$(CH_3)_3N$	$(CH_3)_4NI$
5	Cl_2	$2Na$	$2NaCl$

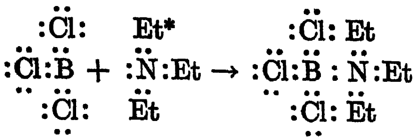
The other attempt to reconcile the proton and the solvent system theories was made by Lewis in 1923 (77). Strictly speaking, it was not an attempt at reconciliation, since both theories were proposed for the first time by Lewis as special cases of his more general and more fundamental theory. Brönsted and Lowry presented their theory independently in the same year, while the general form of the solvent system theory came several years later. The conflict between the two theories has gone on, although the solution to the problem has been at hand since 1923.

C. Outline of the electronic theory of acids and bases

The foundations of an electronic theory of acids and bases have been well laid by Lewis (78). He begins by defining acids and bases in terms of their outstanding experimental property, neutralization. Acids are substances which, like hydrogen ion, neutralize hydroxyl ion or any other base. Bases are substances which, like hydroxyl ion, neutralize hydrogen ion or any other acid. If the definitions are rewarded slightly, they can be based on the experimental facts alone. *Acids are substances which, like hydrochloric acid, neutralize sodium hydroxide or any other base. Bases are substances which, like sodium hydroxide, neutralize hydrochloric acid or any other acid.* Thus worded, the definitions would have applied at any time since the beginning of the classification of acid–base properties. The following experiment, which makes an excellent lecture demonstration, is an interesting example of their generality.

Crystal violet is an indicator which gives the same color change in different solvents. When sodium hydroxide is titrated against hydrochloric acid in water, using crystal violet as the indicator, the solution is yellow when acidic and violet when basic. Pyridine and triethylamine can be titrated in a similar manner against hydrochloric acid, and are therefore bases. If pyridine is dissolved in some comparatively inert solvent, such as chlorobenzene, the same violet color is observed when crystal violet is added. Now if boron trichloride, stannic chloride, or any similar substance soluble in chlorobenzene is added to the basic pyridine solution, the color changes instantly to yellow. Thus boron trichloride and stannic chloride are acids. If triethylamine, acetone, or any other fairly strong base is added, the color changes back to violet. Similar titrations can be performed in other solvents with other indicators and with many other acids and bases none of which contains hydrogen or hydroxyl ions (78). These titrations are strong evidence that there is an inherent difference between the molecules of acids and of bases. This difference is not dependent upon the solvent. It must involve a contrast in atomic structure common to all acids and bases, including hydrogen ion and hydroxyl ion.

The one property common to all acids makes them what Sidgwick (98) calls acceptor molecules. Bases are donor molecules. As Lewis points out, acids and bases coincide completely with Sidgwick's classification of electron-pair acceptors and donors. A base has one or more lone electron-pairs which may be used in coördinate-bond formation. An acid can accept one or more electron-pairs from a base to form coördinate bonds between the acid and base. In terms of the electronic theory: *A base is a base because it can donate an electron-pair to form a coördinate bond. An acid is an acid because it can accept an electron-pair to form a coördinate bond. Neutralization is the formation of the covalent bond between the acid and the base.* For example, when triethylamine neutralizes boron trichloride in chlorobenzene or in the absence of any solvent,



$$\begin{matrix} & :\ddot{\mathrm{Cl}}: & & \mathrm{Et}^{*} & & :\ddot{\mathrm{Cl}}:\mathrm{Et} \\ :\ddot{\mathrm{Cl}}:\ddot{\mathrm{B}} & & + & :\ddot{\mathrm{N}}:\mathrm{Et} & \rightarrow & :\ddot{\mathrm{Cl}}:\ddot{\mathrm{B}}:\ddot{\mathrm{N}}:\mathrm{Et} \\ & :\underset{\cdot\cdot}{\ddot{\mathrm{Cl}}}: & & \ddot{\mathrm{Et}} & & :\underset{\cdot\cdot}{\ddot{\mathrm{Cl}}}:\ddot{\mathrm{Et}} \end{matrix}$$

$^{*}\mathrm{Et} = C_2H_5$

boron trichloride is an acid because it accepts an electron-pair to complete the octet for the boron atom. Triethylamine is a base because the nitrogen atom has an electron-pair which it can offer to form a coördinate bond between the acid and the base. The formation of the covalent bond, —neutralization,—destroys the distinctive properties of both the acid and the base.

The cases of neutralization just discussed take place either in unreactive solvents or in the absence of any solvent. They are less complicated than similar reactions in reactive solvents. Nevertheless, when neutralization and other reactions of these and similar acids and bases in reactive solvents are considered, it is found that they are analogous to corresponding reactions which occur in water in the presence of excess hydrogen ion or hydroxyl ion.

II. THE RÔLE OF THE SOLVENT IN ACID–BASE PROPERTIES

A. Reactions of acids and bases with the solvent

The properties of acids and bases with which we are most familiar from the study of water solutions depend to a great extent upon the presence of the solvent. For example, magnesium reacts slowly with hot water, liberating hydrogen. The reaction is much more rapid in acid solution. The difference must be due to the increased concentration of the solvent cation, the hydrogen ion.[1] At first glance, Lewis' theory seems to have little relation to this large body of experimental behavior with which we are so familiar.

This apparent lack of relationship is the basis of Walden's attack (102) on Lewis' theory. Walden fears that Lewis would destroy the significance of dissociation constants and conductivity measurements. The part played by the solvent would be deliberately eliminated. The oppositeness of acids and bases toward indicators would appear to be purely incidental observations. Unbiased study would have revealed that none of these fears is warranted. We have already seen that the oppositeness of acids and bases toward indicators is by no means a purely incidental observation, and we shall see that Walden's other objections are as groundless, but some justification for Walden's misinterpretation must be ad-

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[1] The term "hydrogen ion" will continue to be used in place of "solvated proton," "hydronium ion", "oxonium ion", or "hydroxonium ion".

mitted. Lewis understands the significance of his theory so well that he has apparently overlooked the necessity of demonstrating its applicability to the familiar data. A sketchy attempt to do this has been made previously by the present author (87). In this paper a more complete presentation will be given.

Water may be regarded as the product of the neutralization of hydrogen ion by hydroxyl ion. The proton is an acid because it tends to accept an electron-pair from a base to complete the *K* shell of electrons. The hydroxyl ion is a base because the oxygen atom can donate an electron-pair to an acid. The formation of the coördinate bond between the proton and the hydroxyl ion is neutralization. The question as to whether the product is actually neutral, in the sense that the donor and acceptor properties of the oxygen and hydrogen atoms are balanced, is probably not of great importance. Sidgwick (98) believes that the oxygen is more powerful as a donor than the hydrogen is as an acceptor. What is more important is that the relative acidity of water can be compared with that of other solvents. For example, glacial acetic acid is more acidic and liquid ammonia more basic than water. In terms of the electronic theory this means that the acetic acid molecule has a greater tendency to accept an electron-pair than does water and that the ammonia molecule has a greater tendency to donate an electron-pair.

When an acid is dissolved in a solvent, the reaction between the acid and the solvent depends primarily upon two factors: the strength of the acid (its tendency to accept an electron pair), and the basic strength of the solvent (its tendency to donate an electron pair). The second factor will be considered in part III. In a given solvent, the strength of the acid can be measured, within the limits of the "leveling effect" of Hantzsch, by means of the equilibrium constant of the reaction with the solvent. For example, if glacial acetic acid, a typical covalent liquid which conducts an electric current poorly, reacts with water according to the equation

$$HC_2H_3O_2 + H_2O \rightleftharpoons H_3O^+ + C_2H_3O_2^-$$

the equilibrium constant,

$$K = \frac{[H_3O^+] \times [C_2H_3O_2^-]}{[HC_2H_3O_2] \times [H_2O]}$$

serves as a semi-quantitative measure of acid strength when compared with similar constants for other acids. This is true only if the acid is not too strong. For strong acids like hydrochloric acid, also a typical covalent compound (possessing only 17 per cent ionic character, according to Pauling (94)), the reaction proceeds completely to the right in a solvent as basic as water.

Similar conclusions apply to other acids. If the reaction occurring when carbon dioxide, a weak acid, is dissolved in water is represented by the equation

$$CO_2 + 2H_2O \rightleftharpoons H_3O^+ + HCO^-$$

the equilibrium constant,

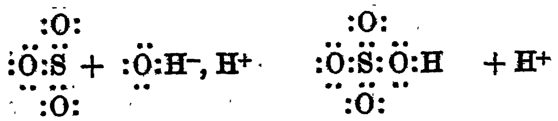
$$K = \frac{[H_3O^+] \times [HCO_3^-]}{[CO_2] \times [H_2O]^2}$$

may serve as a measure of the acid strength of the carbon dioxide. Strong acids like sulfur trioxide act in the same manner as hydrochloric acid. Sulfur trioxide accepts an electron-pair from water just as does the hydrogen in hydrogen chloride, seeking its maximum coördination number of two. The subsequent division into ions is different in that the water molecule is split by the sulfur trioxide, but this is irrelevant to the theory, as we shall see. The reaction

$$SO_3 + 2H_2O \rightleftharpoons H_3O^+ + HSO_4^-$$

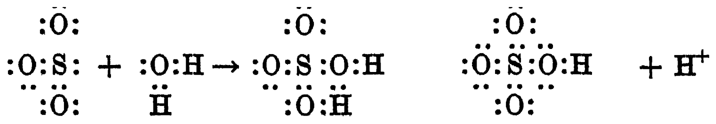
proceeds strongly toward the right. The same considerations hold for acids such as boron chloride, aluminum chloride, or stannic chloride. The boron and aluminum atoms tend to accept an electron-pair to complete their stable shells of eight electrons. The tin atom tends to gain two electron-pairs to complete its stable shell of twelve, as in H_2SnCl_6. There is no valid reason for calling the same type of reaction by two different terms: namely, ionization in the case of hydrochloric acid or acetic acid, and hydrolysis in the case of sulfur trioxide, carbon dioxide, or stannic chloride. The net result is an increase in the concentration of the solvent cations. We shall see that this increased concentration of the solvent cations is responsible for most of the familiar properties of acids and bases in water and similar solvents. It is due to the tendency of an acid to accept electron-pairs from bases in order to complete the characteristic stable electron configuration of the acid.

The actual mechanism may be regarded in either of two ways, as represented by simplified equations for the reaction between sulfur trioxide and water:



$$\begin{array}{c} :O: \\ :\ddot{\underset{\cdot\cdot}{O}}:\ddot{\underset{\cdot\cdot}{S}} \\ :O: \end{array} + \ :\ddot{\underset{\cdot\cdot}{O}}:H^-,\ H^+ \qquad \begin{array}{c} :O: \\ :\ddot{\underset{\cdot\cdot}{O}}:\ddot{\underset{\cdot\cdot}{S}}:\ddot{\underset{\cdot\cdot}{O}}:H \\ :O: \end{array} \quad + H^+$$

a direct reaction between the sulfur trioxide molecule and the hydroxyl ion; or



$$\begin{array}{lllll} \;\;:\overset{\cdot\cdot}{O}: & & \;\;:\overset{\cdot\cdot}{O}: & \;\;:\overset{\cdot\cdot}{O}: & \\ :\underset{\cdot\cdot}{O}:\underset{\cdot\cdot}{S}: + & :\underset{\cdot\cdot}{O}:H \rightarrow & :\underset{\cdot\cdot}{O}:\underset{\cdot\cdot}{S}:O:H & :\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{S}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:H & + H^+ \\ \;\;:O: & \;\;H & \;\;:O:H & \;\;:O: & \end{array}$$

a direct reaction between the sulfur trioxide molecule and the water molecule, followed by ionization. In either case the result is the same. If the acid is strong enough or if the solvent is basic enough, the concentration of the cation characteristic of the solvent is increased.

The corresponding conclusion holds for bases dissolved in ionizable solvents. The solution contains a greater concentration of anions than is present in the pure solvent. The strength of the base in a given solvent can be estimated from the equilibrium constant. For example, when pyridine is dissolved in water, the pyridine molecule acts as a base in donating an electron-pair to the water molecule:

$$C_5H_5N: + H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:H \rightleftharpoons C_5H_5N:H^+ + :\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:H^-$$

The equilibrium constant,

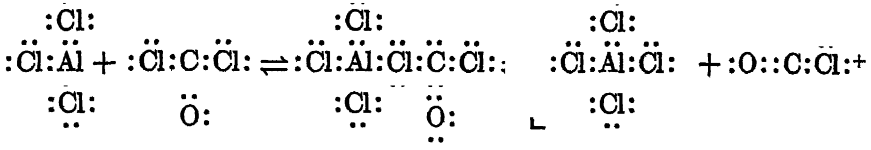
$$K = \frac{[C_5H_5NH^+] \times [OH^-]}{[C_5H_5N] \times [H_2O]}$$

serves to measure the basic strength of the pyridine.

These examples, purposely chosen with water as the solvent, are enough to show that the part played by the solvent is not "deliberately eliminated." Dissociation constants and conductivity measurements still have as much significance as ever. Walden's objections simply do not apply. When a sufficiently strong acid reacts with water, the concentration of the hydrogen ion is increased. When a sufficiently strong base reacts with water, the concentration of the hydroxyl ion is increased. The word "strength" now refers to the tendency of acids to accept electron-pairs and the tendency of bases to donate them, but in a given solvent the strength of an acid or a base, within limits, can be measured by its dissociation constant. There are many examples in the literature to support this conclusion for solvents other than water.

The typically acid properties of aluminum chloride in phosgene (30) are due to this increased concentration of solvent cations. These properties will be considered in section C of this part. Germann found that the conductivity of the aluminum chloride solution was less than that of the calcium salt, $Ca(AlCl_4)_2$, and concluded that the acid was weak.

Aluminum chloride is an acid because it accepts an electron-pair to complete the octet of the aluminum atom. The phosgene is amphoteric and in this reaction is acting as a base. The resulting cation will be solvated, because of the strong tendency of the carbon atom to maintain its octet. The data do not permit certainty as to the mechanism of the reaction between aluminum chloride and phosgene, but if we write the equation as



$$\begin{array}{ccccccc} :\mathrm{Cl}: & & & :\mathrm{Cl}: & & :\mathrm{Cl}: & \\ :\ddot{\mathrm{Cl}}:\ddot{\mathrm{Al}} & + & :\ddot{\mathrm{Cl}}:\mathrm{C}:\ddot{\mathrm{Cl}}: & \rightleftharpoons :\ddot{\mathrm{Cl}}:\ddot{\mathrm{Al}}:\ddot{\mathrm{Cl}}:\ddot{\mathrm{C}}:\ddot{\mathrm{Cl}}: & & :\ddot{\mathrm{Cl}}:\ddot{\mathrm{Al}}:\ddot{\mathrm{Cl}}: & +:\mathrm{O}::\mathrm{C}:\ddot{\mathrm{Cl}}:^{+} \\ :\underset{\cdot\cdot}{\mathrm{Cl}}: & & \ddot{\mathrm{O}}: & :\underset{\cdot\cdot}{\mathrm{Cl}}:\quad \underset{\cdot\cdot}{\ddot{\mathrm{O}}}: & \llcorner & :\underset{\cdot\cdot}{\mathrm{Cl}}: & \end{array}$$

the equilibrium constant,

$$K = \frac{[\mathrm{COCl}^{+}] \times [\mathrm{AlCl}_4^{-}]}{[\mathrm{AlCl}_3] \times [\mathrm{COCl}_2]}$$

will serve as a measure of acid strength when compared with the dissociation constants of other acids in phosgene. According to Germann's conductivity measurements K is small, so aluminum chloride is a fairly weak acid with respect to phosgene. Similar treatment can be given the results of other investigators.

Meerwein (91) has shown that aluminum alcoholates, when dissolved in alcohols, increase the concentration of the solvent cation in the same manner as aluminum chloride does in phosgene:

$$\mathrm{Al(OR)_3} + \mathrm{ROH} \rightarrow \mathrm{HAl(OR)_4}$$

Other acids, such as boron trifluoride, also increase the hydrogen-ion concentration in organic acids. The work of Jander (60) with sulfur dioxide, that of Smith and others with selenium oxychloride, and some of the work in liquid ammonia can be interpreted in a similar way, not only for acids but for bases as well.

The reason for the solvent system definitions of Cady and Elsey is clear. Acids often do increase the concentration of solvent cations; bases often increase the concentration of solvent anions. However, this does not always happen. When acids react with solvents like ether and pyridine, ionization to give a cation characteristic of the solvent is unlikely. Usanovich (101) has shown the similarity in electrical conductivity of solutions of such acids as the arsenic and antimony trichlorides in ether to a solution of sulfuric acid in ether. The conductance of the solutions is greater if the ether is replaced by a stronger base, such as pyridine. Arsenic trichloride reacts with pyridine with liberation of a large amount of heat, forming, after evaporation of the excess pyridine, a crystalline compound $AsCl_3 \cdot C_5H_5N$. It is a familiar fact that pyridine forms crystalline compounds with those salts which, according to Lewis' theory, are fairly strong acids, e.g., zinc chloride. In these cases ionization of the solvent is impossible. The reaction may be represented as follows:

$$C_5H_5N\!: + AsCl_3 \rightleftharpoons C_5H_5N\!:\!AsCl_3 \rightleftharpoons C_5H_5N\!:\!AsCl_2^+ + Cl^-$$

The arsenic atom becomes more negative by gaining a share in the lone electron-pair of the nitrogen atom. The electrical stress can be relieved by the ionization of a chlorine atom. A similar situation holds for ether. An oxonium salt is formed in solution. If we regard the ether and pyridine as solvents, we see that no cation characteristic of the solvent is formed.

We might have drawn the same conclusion from the previously considered reaction between pyridine and water:

$$C_5H_5N\!: + HOH \rightarrow C_5H_5N\!:\!H^+ + OH^-$$

If pyridine is considered the basic solvent and water the acid dissolved in it, there is again no splitting of the solvent to give a cation characteristic of the solvent. The above examples illustrate the inadequacy of the idea that acids and bases can be defined in terms of ions. In certain solvents acids increase the concentration of solvent cations and bases increase the concentration of solvent anions, but in other solvents they do not. These experimental facts do not affect the electronic theory of acids and bases, because it is not stated in terms of ions. It is not even concerned with the mechanism of ionization after neutralization takes place. It recognizes, as does the Brönsted theory, that ionization may not be involved in many reactions of acids and bases.

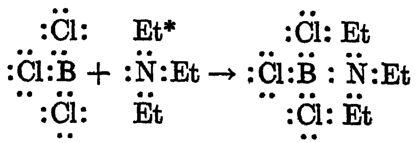
B. Neutralization and the solvent

Neutralization is the formation of the coördinate bond between the acid and the base. The electronic theory gives a real meaning to the word, a meaning of which the Brönsted theory takes no account. The type equation of the Brönsted theory:

$$\text{acid}_1 + \text{base}_2 \rightleftharpoons \text{acid}_2 + \text{base}_1$$

is often assumed to dispose of the concept of neutralization. We shall see in part III that this is not true. The equation may represent the fact that acids or bases will replace weaker acids or bases from their compounds. It does not abolish neutralization.

The acid boron trichloride is neutralized by the base triethylamine when both substances are in the pure liquid or gaseous state:



$$\begin{matrix} & :\overset{\cdot\cdot}{Cl}: & & Et^{*} & & :\overset{\cdot\cdot}{Cl}: & Et \\ :\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}: & \overset{\cdot\cdot}{\underset{\cdot\cdot}{B}} & + & :\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}:Et & \rightarrow & :\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{B}} & :\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}:Et \\ & :\underset{\cdot\cdot}{Cl}: & & Et & & :\underset{\cdot\cdot}{Cl}: & Et \end{matrix}$$

$^{*}Et = C_2H_5$

The product is usually called a molecular or addition compound. Lewis calls it a pseudo-salt, and remarks in passing that such compounds are incapable of ionization. This would seem to be an oversight. The possibility of ionization of one of the chlorine atoms ought to be considered. It may not occur to a great extent in this particular compound, but where sufficient electrical stress is set up, upon the acceptance of a share in another electron-pair by the acid, one would expect ionization to be favored. Such ionization would, of course, be greatly affected by the dielectric constant of the solvent. Three examples of ionization, of the many which could be given, are the following:

$$C_5H_5N: + H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}: \rightarrow C_5H_5N:H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}: \rightarrow C_5H_5N:H^+ + :\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}:^-$$

$$AlCl_3 + COCl_2 \rightarrow ClOCCl{:}AlCl_3 \rightarrow COCl^+ + AlCl_4^-$$

$$SnCl_4 + 2SeOCl_2 \rightarrow (SeOCl)_2SnCl_6 \rightarrow 2SeOCl^+ + SnCl_6^{--}$$

In such cases the product is usually considered a salt. There seems to be no need for the name "pseudo-salt."

Considering only acid-base reactions, solvents may be divided into three classes: (*1*) those that are practically inert toward acids and bases, e.g., benzene, carbon tetrachloride, and chlorobenzene; (*2*) those that are ionizable, e.g., water, ammonia, sulfur dioxide, phosgene, and selenium oxychloride; (*3*) those that do not ionize but do react with acids and bases, e.g., ether and pyridine. If we consider the neutralization of boron trichloride by triethylamine in the three types of solvents, we find that the net result may be the same as when the neutralization occurs in the absence of a solvent.

When the solvent is inert it is merely a diluent and the neutralization product is obtained directly. When the solvent is ionizable, intermediate reactions with the solvent may be observed. If either the acid or the base, or both, are strong enough, they will be at least partially neutralized by the solvent; e.g., if selenium oxychloride is chosen as the solvent,

$$BCl_3 + SeOCl_2 \rightarrow SeOCl^+ + BCl_4^-$$

$$(C_2H_5)_3N + SeOCl_2 \rightarrow (C_2H_5)_3NSeOCl^+ + Cl^-$$

When the two solutions are mixed, neutralization takes place, with the elimination of solvent.

$$SeOCl^+, BCl_4^- + (C_2H_5)_3NSeOCl^+, Cl^- \rightarrow (C_2H_5)_3NBCl_3 + 2SeOCl_2$$

The same product is obtained as when the reaction is carried out directly or in an inert solvent.

When the solvent reacts without ionizing, it reacts with either the acid or the base, but not ordinarily with both. Such solvents are usually not amphoteric. For example, if boron trichloride is neutralized by triethylamine in ether, the boron trichloride would react with the ether, but the triethylamine would not. The oxygen atom in the ether can donate an electron-pair to form an oxonium bond, but the hydrogen atoms in ether have little tendency to form hydrogen bonds (94).

$$BCl_3 + (C_2H_5)_2O \rightarrow (C_2H_5)_2OBCl_3$$

When triethylamine is added, it merely displaces the weaker base and the resulting product is the same as before.

$$(C_2H_5)_2OBCl_3 + (C_2H_5)_3N \rightarrow (C_2H_5)_3NBCl_3 + (C_2H_5)_2O$$

In all four cases the neutralization product is the same.

However, it would be dangerous to generalize from this observation, since the reactions depend upon the relative strengths of the various acids and bases involved. Probably the most that ought to be attempted is the classification of solvents as inert, amphoteric, and non-amphoteric. The reactive non-ionizing solvents should be called non-amphoteric rather than either acidic or basic, because the ionizing solvents may be predominantly acidic or basic while retaining the possibility of amphoteric behavior under proper conditions.

C. Typical reactions of acids and bases

Typical properties of acids and bases are usually taken to be those which are observed in water solutions of acids and bases. Most of these properties are due to the increased concentration of solvent cation or solvent anion caused by the presence of the acid or base. The most familiar reactions dependent upon this effect probably are the reactions between the free elements and solutions of acids and bases, electrolysis, and the reactions of amphoteric substances. The first is the only one which requires further discussion before similar reactions in other solvents are considered.

Active metals like sodium and calcium are oxidized by pure water. Active non-metals like chlorine and sulfur also react with water, but the reactions are more complex. Chlorine reacts to give hydrochloric and hypochlorous acids. Sulfur reacts slowly when heated with water, to give several products (25). These reactions may be considered as due to the presence of hydrogen ions and hydroxyl ions. The hydrogen ions oxidize active metals and become free hydrogen. The reaction of hydroxyl ions with active non-metals is not so simple. This is probably due to the fact that the oxygen atom has a greater attraction for electrons than any other atom except fluorine. Many metals will reduce hydrogen ion, but only one non-metal, fluorine, will oxidize hydroxyl ion under ordinary circumstances. Chlorine and sulfur are unable to remove electrons completely from the hydroxyl ion.

These reactions proceed much more rapidly when the hydrogen-ion or hydroxyl-ion concentration is increased by the addition of an acid or base. This increase in rate seems to be a mass action effect, e.g., in the reaction

$$Mg + 2H_3O^+ \rightarrow Mg^{++} + H_2 + 2H_2O$$

increasing the concentration of the hydrogen ion will have the same effect whether it is done "directly" by adding hydrogen chloride, or indirectly by adding sulfur trioxide to the water. In like manner, it makes no difference how the hydroxyl-ion concentration is increased. It may be brought about by adding the ions directly through the addition of sodium hydroxide or it may be done indirectly by adding triethylamine to the water:

$$(C_2H_5)_3N\!: + H\!:\!\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}\!:\!H \rightarrow (C_2H_5)_3N\!:\!H^+ + :\!\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}\!:\!H^-$$

It is worth noting at this point that, in these typical reactions, hydrogen ion and hydroxyl ion are not acting strictly as acid and base. The hydrogen ion acts as an oxidizing agent, removing electrons completely from the metals which react with it. The hydroxyl ion acts as a reducing agent toward the only element capable of removing electrons from it:

$$2F_2 + 4OH^- \rightarrow 4F^- + O_2 + 2H_2O$$

Such reactions, as well as those of electrolysis and of amphoteric behavior, have been observed in other solvents. Reactions which occur in ammonia (22 to 25), sulfur dioxide (2, 57 to 65, 104), acetic acid (11 to 15, 36), hydrogen sulfide (106), hydrogen fluoride (26), phosgene (29 to 31), selenium oxychloride (100, 107), alcohols (53, 91), and sulfuric acid (43, 44) are analogous to those which take place in water. Some of them have been interpreted according to the solvent system theory, others according to the proton theory. All of them may be understood more clearly on the basis of the electronic theory of acids and bases. Only a few examples will be discussed here.

A solution of aluminum chloride in phosgene dissolves metals with the liberation of carbon monoxide. According to Lewis' theory, the aluminum chloride is an acid and accepts an electron-pair from the solvent. The resulting electrical stress favors the ionization which increases the concentration of solvent cation. The solvent cation oxidizes the metal, and carbon monoxide is produced:

$$COCl^+ + Ca \rightarrow CO + Cl^- + Ca^{++}$$

or

$$CO(AlCl_4) + Ca \rightarrow CO + Ca(AlCl_4)$$

This behavior is analogous to that of sulfur trioxide when dissolved in water. The sulfur trioxide accepts an electron-pair from the solvent, and the concentration of the solvent cation is greatly increased. The solvent cation oxidizes the metal, and hydrogen is produced.

Similar reactions are observed in the other solvents listed above. Those in selenium oxychloride are particularly interesting since, as with phosgene, no protons are involved. Although the reported value of its solvent conductance (66) seems to be too high, the ion concentrations in pure selenium oxychloride are likely to be relatively great. It would appear also that the solvent cation is a stronger oxidizing agent than hydrogen ion. Yet when an acid like stannic chloride is dissolved in selenium oxychloride (100), the result is as expected. The solution reacts more vigorously with metals than does the pure solvent, because of the increased concentration of solvent cation:

$$SnCl_4 + 2SeOCl_2 \rightarrow (SeOCl)_2^+, SnCl_6^{--}$$

Jander has not yet investigated this effect in sulfur dioxide. One would expect that the same behavior would be observed. Sulfur monoxide should be produced when metals react with acid solutions of sulfur dioxide. One method of preparing sulfur monoxide (95, 20) is by the action of sulfonyl chloride on metals. The effect of strong acids, such as sulfur trioxide and boron trichloride, should be to increase the rate of formation of sulfur monoxide.

Corresponding reactions for bases, i.e., the action of the solvent anion as a reducing agent, are observed in liquid ammonia. Whereas in water fluorine is the only active non-metal which can oxidize hydroxyl ion, in ammonia the other halogens can oxidize the amide ion. Iodine reacts with amide ion, just as fluorine reacts with hydroxyl ion (4, 25):

$$3I_2 + 6NH_2^- \rightarrow 6I^- + 4NH_3 + N_2$$

The reaction is more vigorous in a potassium amide solution than in ammonia alone. Other reactions with non-metals such as sulfur, involving an increased concentration of solvent anion, are more complex.

They are similar to those in water, since, like the hydroxyl ion, the amide ion does not readily lose electrons completely.

When electrolysis reactions in various solvents are considered, the conditions that determine which ion is to be discharged at either electrode are such that no conclusions can be drawn with regard to acid-base phenomena. For example, hydrogen is discharged at the cathode when an aqueous solution of an acid is electrolyzed, but hydrogen is also produced when an aqueous solution of sodium sulfate or of sodium hydroxide is electrolyzed. The most that can be said for the results of electrolysis is that they are consistent with what has just been said concerning cations and anions characteristic of the solvent. Carbon monoxide is discharged at the cathode when a solution of aluminum chloride in phosgene is electrolyzed. Selenium dioxide and selenium monochloride are produced at the cathode upon electrolysis of a solution of stannic chloride in selenium oxychloride.

Interpretation of the work of Bagster and Cooling (2) according to the electronic theory of acids and bases would indicate that they unknowingly produced sulfur monoxide by electrolysis. Their interest in demonstrating the existence of the hydronium ion apparently caused them to overlook indications which might have led to the discovery of sulfur monoxide. When water was added to liquid sulfur dioxide and gaseous hydrogen bromide was passed in, two liquid layers were formed. Electrolysis of the sulfur dioxide layer yielded hydrogen at the cathode and bromine at the anode. Water collected at the cathode in proportion to the amount of silver deposited in a coulometer, but the amount of hydrogen discharged was less than expected, if the only ion being discharged was the H_3O^+ ion. This would indicate that $SO(H_2O)_2^{++}$ ions were being discharged as well as hydronium ions. Bagster and Cooling were not able to account for the smaller amount of hydrogen, but they did siphon off the sulfur dioxide layer from the water layer and try electrolysis of the sulfur dioxide alone. The conductance fell rapidly and sulfur was deposited at the cathode, but no water. This would indicate that the (solvated) SO^{++} ion was being discharged to form sulfur monoxide. Sulfur monoxide decomposes readily to form sulfur and sulfur dioxide.

Amphoteric reactions such as those of the hydroxides of aluminum and zinc also occur in other solvents. When potassium hydroxide is added to insoluble aluminum hydroxide in water, the following reaction takes place:

$$Al(OH)_3 + OH^- \rightarrow Al(OH)_4^-$$

The $Al(OH)_4^-$ ion is soluble. It is formed because the aluminum hydroxide is acidic, in that the aluminum atom accepts an electron-pair to complete its octet. An analogous reaction takes place in liquid ammonia (3), when insoluble aluminum amide is dissolved by potassium amide.

$$Al(NH_2)_3 + NH_2^- \rightarrow Al(NH_2)_4^-$$

The zinc ion is also a fairly strong acid, and its insoluble compounds with solvent anions are often amphoteric. For example, in water, liquid ammonia (25), and glacial acetic acid (15) the following reactions occur:

$$Zn(OH)_2 + 2OH^- \rightarrow Zn(OH)_4^{--} \quad \text{(in water)}$$

$$Zn(NH_2)_2 + 2NH_2^- \rightarrow Zn(NH_2)_4^{--} \quad \text{(in ammonia)}$$

$$Zn(C_2H_3O_2)_2 + 2C_2H_3O_2^- \rightarrow Zn(C_2H_3O_2)_4^{--} \quad \text{(in acetic acid)}$$

The complex anions formed are soluble in each case. Such reactions occur because zinc and aluminum ions are fairly strong acids, having considerable tendency to complete their octets. Thus the electronic theory of acids and bases provides a consistent explanation of all such phenomena.

One other example of typical basic properties will be discussed briefly. Zinc, aluminum, and a few other metals are dissolved in water and in liquid ammonia (3) by bases as well as by acids. In both solvents hydrogen is liberated and the same complex anions are formed as when the insoluble solvent anion compounds are dissolved by bases:

$$Zn + 2KOH + 2H_2O \rightarrow K_2Zn(OH)_4 + H_2$$

$$Zn + 2KNH_2 + 2NH_3 \rightarrow K_2Zn(NH_2)_4 + H_2$$

$$2Al + 2KOH + 6H_2O \rightarrow 2KAl(OH)_4 + 3H_2$$

$$2Al + 2KNH_2 + 6NH_3 \rightarrow 2KAl(NH_2)_4 + 3H_2$$

Bergstrom (3) has suggested that the mechanism of the reaction between aluminum and potassium amide in liquid ammonia is as follows:

$$Al + 3KNH_2 \rightarrow Al(NH_2)_3 + 3K$$

The potassium ion is reduced, in spite of the fact that it has less affinity for electrons than the aluminum atom, because the insolubility of the aluminum amide drives the equilibrium to the right. The aluminum amide then reacts with amide ion to form the complex $Al(NH_2)_4^-$ ion, which still keeps the concentration of aluminum ion very low:

$$Al(NH_2)_3 + KNH_2 \rightarrow KAl(NH_2)_4$$

The reaction between the free potassium and the solvent is one which is ordinarily slow, but it is catalyzed by the aluminum:

$$6K + 6NH_3 \rightarrow 3H_2 + 6KNH_2$$

Bergstrom suggests that the mechanism of similar reactions in water is the same, and cites the fact that the blue color observed when a magnesium rod is dipped into fused potassium hydroxide is an indication of the presence of free potassium from the reaction

$$Mg + 2KOH \rightarrow Mg(OH)_2 + 2K$$

Such reactions probably are not general enough to warrant calling them typical basic reactions.

All the reactions so far discussed in this section have involved amphoteric solvents which, it is assumed, may ionize like water. Most of the reactions involve the same effect of acids and bases on the concentration of solvent cations or solvent anions that is observed in water. They are "typical" reactions only because they resemble those in water, with which we are more familiar. We should expect, therefore, that acid–base properties in inert solvents such as benzene, or in non-amphoteric solvents such as pyridine, would not be "typical." In such solvents there is no possibility of a "typical" increase in solvent cations or anions upon the addition of acids or bases. Ions are produced when acids and bases react with non-amphoteric solvents such as pyridine and ether, but the ions formed are not "characteristic" of the solvent. Little more needs to be said here than in section A of this part, except by way of indicating the possibilities of a wider application of Lewis' theory. Only one example will be given. The conductance curves of silver salts in pyridine (86) and in amines (18, 19) are abnormal. A possible explanation lies in the fact that the silver ion is a fairly strong acid. A familiar indication of this is the formation of the $Ag(NH_3)_2^+$ ion in water. The silver ion can accept two electron-pairs, each involving one molecule of a neutral base, such as ammonia, pyridine, or amines.

As a rule no ions are produced when acids and bases are dissolved in inert solvents. The assumption of "protective coatings" (39) to explain the absence of a reaction between metals and a solution of hydrogen chloride in benzene is unnecessary. In water metals react more rapidly when an acid is present, because of the increased concentration of solvent cations. The metal reacts slowly with water even in the absence of the acid, but no such reaction takes place in benzene because there are no solvent cations with which the metal can react. The statement is sometimes made that acids dissolved in inert solvents do not react with carbonates. The reaction with carbonates is one which does not necessarily depend on solvent cations. It depends on the strength of the acid required to displace the weaker carbon dioxide from its compound. Lewis has shown (78) that a strong acid like boron trichloride will displace carbon dioxide from sodium carbonate in a mixture of carbon tetrachloride and acetone.

The fact that acids are not usually ionized in inert solvents permits a better determination of their relative strength than is possible in water. In water perchloric, hydriodic, hydrobromic, hydrochloric, and nitric acids are all practically 100 per cent ionized, thus appearing to be of equal strength. They all have such a strong tendency to accept an electron-pair that the reaction with water goes to completion. Because of this "leveling effect," as Hantzsch called it, there can be no stronger acid than hydrogen ion in water. Any acid much stronger than hydrogen ion will displace it completely. One way in which the strengths of such acids can be compared is by measuring them in some inert solvent. This has been done by Hantzsch (47, 48, 49), who found a great difference in the strengths of several strong hydrogen acids. Perchloric acid is the strongest, followed in order by hydriodic, hydrobromic, hydrochloric, and nitric acids.

We have seen that Walden's fears that Lewis would deliberately eliminate the important part played by the solvent in acid–base properties were entirely groundless. Lewis' acids and bases, dissolved in suitable amphoteric solvents, have the "typical" properties of acids and bases. These "typical" properties are the properties with which we are familiar from our study of water chemistry. Now that we are beginning to branch out into other fields, we may expect to find increasingly that the electronic theory of acids and bases is the only one so far proposed which is at all adequate.

III. FURTHER IMPLICATIONS OF THE ELECTRONIC THEORY OF ACIDS AND BASES

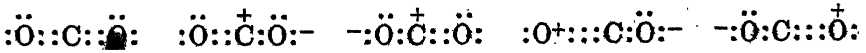
A. *The extent of acid–base phenomena*

The measure of correlation to be effected by the electronic theory of acids and bases can be surmised by recalling that all the substances that Sidgwick (98) called electron-pair acceptors and donors are really acids and bases (78). There is no need for any other name for them. The list of bases compiled by Brönsted and his followers is identical as far as it goes with that of Lewis, but the clear-cut recognition of the reason for their basicity is denied the followers of Brönsted by their devotion to the "cult of the proton". "To restrict the group of acids to those substances which contain hydrogen interferes as seriously with the systematic understanding of chemistry as would the restriction of the term oxidizing agent to substances containing oxygen" (78). There is little doubt that the recognition of acids as electron-pair acceptors and bases as electron-pair donors will lead to as great a degree of systematization as did the recognition of oxidizing agents as electron-acceptors and reducing agents as electron-donors. Furthermore, the possibility of correlating the two types of phenomena now appears for the first time. This will be attempted in section D of this part.

Lewis has pointed out that there are only a small number of elements whose atoms can contribute basic properties to a molecule. These are principally the members of the nitrogen, oxygen, and fluorine families. The atoms of the "inert" gases can also act as bases (6, 93), by donating one or more pairs of their outer octets to sufficiently strong acids. On the other hand, all the elements except the rare gases and the heavier members of the alkali and alkaline-earth families can act as acids. Some of them are extremely weak, but even sodium ion has some tendency to accept an electron-pair. The atoms may manifest their acidic or basic tendencies in various ways, as atoms, ions, or molecules. For example, sulfur trioxide is a strong acid because in it the sulfur atom has a great tendency to accept an electron-pair to complete a stable octet (e.g., in becoming a sulfate ion), but the sulfide ion is a fairly strong base. Davy was not so far from the truth when he said that acidity does not depend upon a particular element, but upon the arrangement of atoms (38).

As a rule, consideration of the electronic structure will reveal whether a molecule is acidic or basic and often will give an idea as to its strength as an acid or base. It is found experimentally that these acids and bases, given sufficient difference in strength, combine "without impediment" (78). Lewis calls such acids and bases primary. No heat of activation is required for the neutralization of a primary acid and a primary base. On the other hand, certain substances which experimentally behave like acids, e.g., carbon dioxide and organic acid halides, have electronic formulas which, as usually written, do not show the possibility of their acting as electron-pair acceptors. Neutralization of these substances is always measurably slow (78, 79, 80). Such acids (and bases) are called secondary by Lewis. The neutralization of secondary acids and secondary bases requires heat of activation. Lewis suggests that these secondary acids and bases are not acids or bases in their normal states of lowest energy, as represented by the electronic formulas usually written, but may become acids and bases through excitation. These substances act like acids and bases,—except that their neutralization is slow,—but their electronic formulas do not indicate such behavior. Perhaps some of the difficulty lies in the formulas. This conclusion is supported by the work of Pauling (94).

According to Pauling, resonance in the carbon dioxide molecule occurs among five electronic structures:



$$:\ddot{\mathrm{O}}::\mathrm{C}::\ddot{\mathrm{O}}: \qquad :\ddot{\mathrm{O}}::\overset{+}{\mathrm{C}}:\ddot{\mathrm{O}}:- \qquad -:\ddot{\mathrm{O}}:\overset{+}{\mathrm{C}}::\ddot{\mathrm{O}}: \qquad :\mathrm{O}^{+}:::\mathrm{C}:\ddot{\mathrm{O}}:- \qquad -:\ddot{\mathrm{O}}:\mathrm{C}:::\overset{+}{\mathrm{O}}:$$

The carbon atom in the second and third arrangements of electrons can accept an electron-pair to complete a stable octet. Consideration of resonance in the carbon dioxide molecule brings the electronic formula into correspondence with the experimental behavior of carbon dioxide as a secondary acid. This is also true of the organic acid halides.

It has been known for some time that the properties of the carbon-oxygen double bond often are not well represented by the usual formula. Lowry suggested in 1923 that, instead of representing the structure of the carbonyl group of aldehydes and ketones as in $R_2C::\ddot{O}:$, the formula $R_2C^+:\underset{\cdot\cdot}{\ddot{O}}:^-$ should be used. Pauling shows that, in the resonance between the two, the latter structure is almost as significant as the former. In the semi-ionic structure the carbon atom can accept an electron-pair, so that the possibility of acidic behavior is indicated. Compounds containing such double bonds should be amphoteric. In terms of the electronic theory, the familiar reactions of aldehydes confirm this conclusion. The organic acid halides exhibit more definite "typical" acid behavior in one respect, because they can react with water to increase the concentration of hydrogen ions.

Another type of "secondary" behavior is evident when amphoteric molecules partially or wholly neutralize each other, or when molecules are neutralized by the solvent in which they are placed. For example, the acid A may be dissolved in the weak base B and be neutralized, in that the stable electron configuration of the acidic atom has been attained by acceptance of electron-pairs from the base. Yet if a stronger base B^1 is added, the stronger base will replace the weaker one in combination with the acid:

$$B^1 + AB \rightarrow AB^1 + A$$

Such reactions usually require activation, but in many cases this is small enough to be ignored (78).

Another extension of the idea of acids and bases involves acidic and basic radicals in organic compounds (78). For example, the familiar ortho-para-directing groups for substitutions in the benzene ring are basic. They have electron-pairs which they can share with a neighboring atom. The meta-directing groups are acidic. They can share an electron-pair possessed by a neighboring atom. The action of the acid and basic radicals in directing substituents is explained in terms of resonance by Ingold (55) and Pauling (94).

As has already been indicated, the treatment of amphoteric behavior is much more satisfactory on the basis of the electronic theory. Amphoterism is widespread. As Hantzsch has shown experimentally (49, 51), even strong acids like nitric acid may be amphoteric. Hydrogen chloride is also amphoteric. It acts as a base toward many strong acids like stannic chloride, in forming such compounds as H_2SnCl_6. This is readily accounted for, since one or more atoms in a molecule may be able to accept electron-pairs while others may donate them. The amphoteric behavior of many solvents has been explained by Sidgwick (98) on this basis. It accounts for the association which is typical of amphoteric solvents. Ether and pyridine are not associated, because they are not amphoteric. Obviously, a very large number of substances can act either as acids or as bases, depending on the conditions under which they react.

These examples are only an indication of the widespread applicability of the electronic theory of acids and bases.

B. Strengths of acids and bases

According to Lewis' theory, the strength of an acid corresponds to its tendency to accept an electron-pair from a base. The strength of a base corresponds to its tendency to donate an electron-pair to an acid. Strong acids and bases combine with each other to form stable compounds. Strong acids and bases may combine with weak ones to form fairly stable compounds, but weak acids and bases do not ordinarily form stable compounds. In general a strong acid, A^1, will replace a weaker one from combination with a base:

$$A^1 + AB \rightarrow A^1B + A$$

A strong base, B^1, will replace a weaker one from combination with an acid:

$$B^1 + AB \rightarrow B^1A + B$$

For example, stannic chloride dissolved in selenium oxychloride combines with the solvent. When a stronger base than selenium oxychloride, such as pyridine, is added, the selenium oxychloride is replaced and a more stable compound is formed (100).

This conception of replacement is often equivalent to the Brönsted formulation,

$$A_1 + B_2 \rightarrow A_2 + B_1$$

but is more exact. Furthermore, it does not require abandoning the concept of neutralization. Neutralization occurs when an acid combines with a base, but a stronger acid will replace the first one. This sequence may be illustrated as follows:

$$HCl + H_2O \rightarrow H_3O^+ + Cl^-$$

The formation of the coördinate bond between the water molecule and the hydrogen chloride, by means of the "hydrogen bond," results in such great electrical stress that practically all of the molecules thus formed split into ions. Neutralization has occurred through the formation of the coördinate bond. The subsequent behavior is irrelevant. The "acidic" reaction of the solution toward litmus and some other indicators is only relative. The solution is merely acidic with respect to pure water. If a stronger base than water is added, the water will be displaced from its combination with the proton:

$$NH_3 + H_3O^+ \rightarrow NH_4^+ + H_2O$$

$$B^1 + AB \rightarrow AB^1 + B$$

The ammonium ion is more stable than the hydronium ion.

With proper precautions, such replacement reactions can often be used to measure acid or base strength, as we have already seen in section A of part II. An interesting example of this method is given by the work of Sisler and Audrieth on the action of liquid ammonia on sulfur trioxide addition compounds (99). Although they did not think of it as such, their work seems to be an excellent illustration of the replacement of bases by a stronger base. Sulfur trioxide is one of the strongest acids known. It forms compounds even with such weak bases as hydrogen chloride. Compounds of sulfur trioxide with the five bases pyridine, dimethylaniline, dioxane, sodium chloride, and hydrogen chloride were added to liquid ammonia, a stronger base. The reactions were more rapid in the order given, those between ammonia and the sodium chloride–sulfur trioxide and the hydrogen chloride–sulfur trioxide addition compounds being extremely vigorous.

A convenient way of using the replacement method may be to employ an indicator as one of the acids or bases (12, 32, 40, 42, 49, 50, 68, 71). Among methods of estimating acid or base strength are the determination of dissociation constants by other means, such as conductivity measurements (19, 70, 103, and others) and the measurement of catalytic activity (48, 49). By the latter method Hantzsch showed that the order of strength of some hydrogen acids in inert solvents is as follows: $HClO_4 > HI > HBr > RSO_2OH > HCl > HNO_3 > CCl_3COOH$. Kolthoff and Willman (70) have found the same order for perchloric, hydrobromic, hydrochloric, and nitric acids in glacial acetic acid by the conductance method. Another method which may offer promise in some cases involves electromotive force measurements (34, 96). It is interesting to note that the "anomalous" conductance curves cited by Hall and Werner (34) have since been accounted for by the work of Fuoss and Kraus (27, 28, 85).

While in general it seems possible to arrange acids or bases in a sequence of strengths, the situation is far from clarified. Three of the principal sources of confusion are the leveling effect, the existence of specific reactions such as those cited by Lewis (78, 81), and the effect of concentration. The leveling effect makes it impossible to differentiate between the strengths of acids such as perchloric and hydrochloric in dilute aqueous solution. Both are strong enough acids and water is strong enough as a base so that the reactions go to completion in dilute solution. The more basic a solvent is, the greater will be its leveling effect upon acids. For example, in liquid ammonia acetic acid appears to be as strong as hydrogen chloride (96). Ammonia is a strong enough base so that the reaction to form ammonium and acetate ions is practically complete. On the other hand, when the solvent is weak enough as a base the differences begin to appear again. In acetic acid the difference between perchloric acid, hydrogen bromide, hydrogen chloride, and other acids becomes obvious (12, 70). The use of an inert solvent, when possible, may overcome the difficulty arising from the leveling effect. This may not be necessary if work in a particular solvent can be confined within certain limits. The order in strength of many weak acids is the same in water as it is in inert solvents such as chlorobenzene (32).

The only important criticism of Lewis' theory has been made by Shatenstein (97). He maintains that Lewis' emphasis upon specific reactions is inconsistent with his "phenomenological criterion" that an acid or base will replace a weaker acid or base from its compounds. If these exceptions are as widespread as Lewis seems to indicate, this criticism appears to be a valid one, unless some consistent reason for their appearance as exceptions can be found. Perhaps in some instances the effect of concentration has not been properly considered. This seems to be true in one case cited by Lewis as an example of specific behavior.

Lewis states (78) that many heavy-metal ions, like silver ion, are stronger acids toward ammonia than toward "water or hydroxyl ion." He says that these ions have little tendency to combine with hydroxyl ion, but a strong tendency to combine with ammonia. This is said to occur in spite of the fact that hydroxyl ion is a slightly stronger base toward hydrogen ion than is ammonia, as shown by the equilibrium constant of the reaction

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$$

Lewis develops the idea, using silver ion as an example, as showing how impossible it is to arrange acids in a single monotonic order. This case is one of the principal reasons given by him for believing that relative strength depends upon both the solvent and the particular acid or base used for reference.

The present author believes that Lewis is mistaken in this instance.

If this is true, it seems that such a mistake may arise from a failure to consider carefully enough the effect of concentration on the equilibria involved. Oxidizing and reducing agents are arranged in a series according to their strength at a given concentration. Looking at the electrochemical series, we say that potassium is a stronger reducing agent than aluminum. Yet in liquid ammonia aluminum may reduce potassium ions. In the equilibrium

$$Al + 3KNH_2 \rightleftharpoons Al(NH_2)_3 + 3K$$

the reaction is practically complete to the right, because the aluminum amide is insoluble so that the concentration of aluminum ions is kept low. Such apparent exceptions to the electrochemical series are fairly common, and many other examples could be given, such as the reaction between silver and hydriodic acid and the reversal of a Daniell cell. If the effect of concentration were not understood, the electrochemical series would have been discarded long ago. The situation seems to be similar with regard to acids and bases.

When the effect of concentration is carefully considered, it would appear that the behavior of the heavy-metal ions toward hydroxyl ion and ammonia does not support Lewis' contention that it is impossible to arrange acids and bases in a single monotonic order. In the first place, Lewis fails to distinguish between the basic strength of water and the hydroxyl ion (78, page 299). He says that in aqueous solution, e.g., in a solution of silver nitrate, the heavy-metal ions which combine with ammonia have little tendency to combine with hydroxyl ions. It is true that some of these ions do not displace hydrogen ions from water by combining with hydroxyl ions to any great extent. This merely indicates that they are not strong acids compared to hydrogen ion. A careful distinction must be made between the reaction of these ions with water and their reaction with hydroxyl ion. Both hydroxyl ion and ammonia are much stronger bases than water. No comparison between ammonia and hydroxyl ion can be attempted unless the concentrations of each are comparable. When this is the case, we find that the tendency of the heavy-metal ions to combine with hydroxyl ion is comparable with their tendency to combine with ammonia. For example, cupric ions form a precipitate with hydroxyl ions. The principal difference lies in the fact that one base is charged and the other is not. The negative charge on the hydroxyl ion usually prevents the cation from coördinating as many hydroxyl ions as it does ammonia molecules.

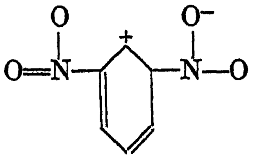
Familiarity with the action of ammonia solution in first precipitating the hydroxides of these heavy-metal ions and then dissolving them upon further addition of ammonia is likely to lead one astray, unless the effects of variation in the concentrations of the various ions and molecules are all taken into account. When this is done, it is found that the metal ions which combine with ammonia are not stronger acids toward ammonia than toward hydroxyl ion. For example, when an ammonia solution is added to a solution of silver nitrate a drop at a time, a brown precipitate forms. This precipitate is probably silver hydroxide, which when dehydrated becomes black silver oxide. Whether its formula is AgOH or not, its precipitation is due to the presence of hydroxyl ion in small concentration, produced by the reaction

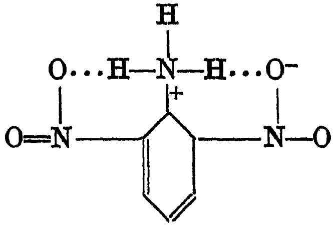
$$NH_3 + H_2O \rightarrow NH_4^+ + OH^-$$

The equilibrium is such that in ordinary use the concentration of ammonia is much higher than the concentration of hydroxyl ion. The formation of the precipitate with the initial addition of ammonia solution shows that hydroxyl ion is a stronger base than ammonia toward silver ion, just as it is toward hydrogen ion. When more ammonia solution is added, the mixture is much more concentrated in ammonia with respect to hydroxyl ion, and the precipitate dissolves to form the silver ammonia complex. This reaction takes place, despite the fact that the hydroxyl ion is a slightly stronger base than ammonia, because the concentration of ammonia has been so greatly increased. It is comparable to the reversal of a Daniell cell or to the reaction between silver and hydriodic acid, which takes place even though silver is below hydrogen in the electrochemical series.

If only a few drops of ammonia solution have been added in excess, addition of a few drops of sodium hydroxide solution brings the precipitate of silver hydroxide back. Even after a large amount of ammonia has been added, the precipitate can be brought back if the proportion of hydroxyl ion to ammonia is made high enough by dissolving solid sodium hydroxide in the solution. When the concentration of hydroxyl ion is maintained by an excess of solid sodium hydroxide, the silver hydroxide precipitate does not dissolve at all. When concentrated ammonia solution is added, vigorous bubbling occurs as the solution is shaken, owing to the escape of some of the ammonia because of the high hydroxyl-ion concentration, and the precipitate turns black; but it does not dissolve so long as the hydroxyl-ion concentration is maintained by an excess of solid sodium hydroxide. After enough water is added to dissolve the sodium hydroxide, the black precipitate redissolves when sufficient ammonia solution is added to make the ammonia concentration large compared to the hydroxyl-ion concentration. Thus it would seem that the behavior of the heavy-metal ions towards hydroxyl ion and ammonia does not support the conclusion that acids and bases cannot be arranged in a single order of strength. When the effect of changing concentration upon such reactions is considered, encouragement is given the feeling that an order of acidic and basic strength which will be at least as reliable as the electrochemical series may be worked out.

The problem seems at present more difficult for acids and bases than for oxidizing and reducing agents. Lewis gives other examples of specific reactions. His examples involving chelation are especially interesting (78, 81). For example, ammonia is a weaker base than triethylamine, yet it behaves as a much stronger one toward *m*-dinitrobenzene. Double chelation is the explanation advanced by Lewis and Seaborg (81):





II

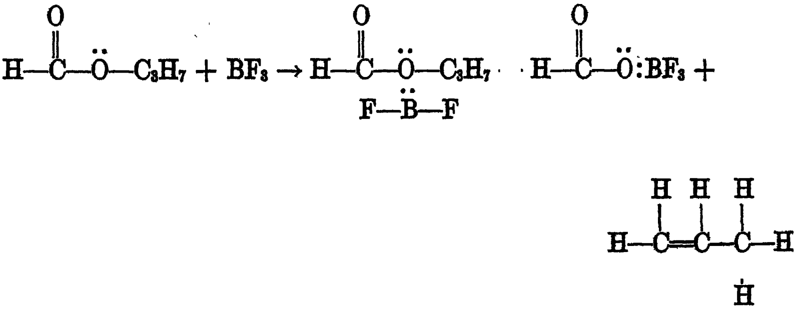
Formula I represents one of the resonating structures of *m*-dinitrobenzene. Formula II represents the compound formed upon the addition of ammonia. Lewis' papers may be consulted for other examples of such effects due to chelation. It also seems to be true that the relative strengths of two bases, one neutral and one charged, e.g., acetate ion and aniline, are affected by changes in solvent, whereas the relative strengths of two bases of the same electrical type are not (42). Another complicating factor for solutions of acids and bases is the influence of the dielectric constant of the solvent. In a solvent of high dielectric constant, dissociation may take place, whereas the same substance in a solvent such as benzene may be highly associated. The degree of dissociation depends upon the difference in strength between the acid or base and the solvent as well as upon the dielectric constant. Perhaps for the time being the problem should be simplified by accepting certain restrictions, such as limiting comparisons to the same charge type.

With these limitations and by proper precautions as to the leveling effect it would seem possible to work out a series of acid and base strengths which would be as useful as the electrochemical series. However, the experimental evidence is not yet complete enough to permit reaching a definite decision at the present time. Perhaps there is no decision to be made. There seems to be little real difference between saying that it is impossible to arrange acids and bases in an exact order because of certain specific reactions, but that in general it can be done for practical purposes, and saying that it is possible if we understand the reason for certain exceptions.

C. Catalysis

One property of acids and bases which has not yet been considered is their catalytic action. Hantzsch (43 to 51) was one of the first to show that acid catalysis does not necessarily depend upon hydrogen-ion concentration, even for hydrogen acids. The Brönsted theory has dealt with a limited phase of acid–base catalysis in terms of mathematics which gives little understanding of the mechanism (8, 82). When we consider the effect of strong acids like the boron and aluminum chlorides on organic syntheses, we realize what a large amount of work remains to be done. Only a few examples of acidic and basic catalysis will be given to show how the mechanism may be better understood by means of the electronic theory.

Benzene can be alkylated by esters in the presence of aluminum chloride or boron trifluoride (89). Alcohols are supposed to react with benzene by dehydration and condensation of the olefin into the benzene nucleus. Esters appear to react in a similar manner:

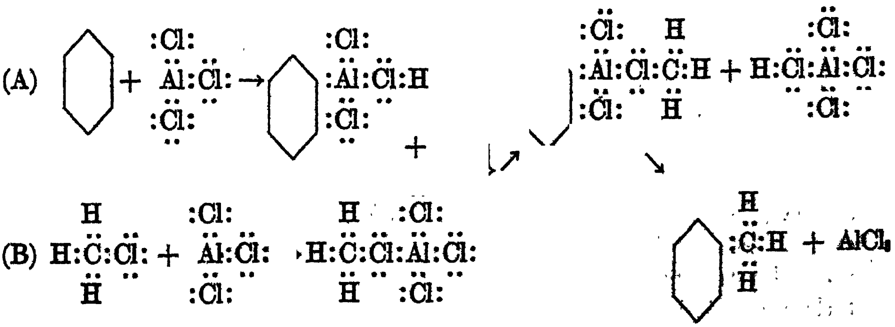


$$\mathrm{H{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\ddot{O}{-}C_3H_7 + BF_3 \rightarrow H{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle F{-}B{-}F}{\cdot\cdot}}{\ddot{O}}{-}C_3H_7 \cdot H{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\ddot{O}{:}BF_3 +}$$

$$\mathrm{H{-}\overset{\overset{\displaystyle H}{|}}{C}{=}\overset{\overset{\displaystyle H}{|}}{C}{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}{-}H}$$

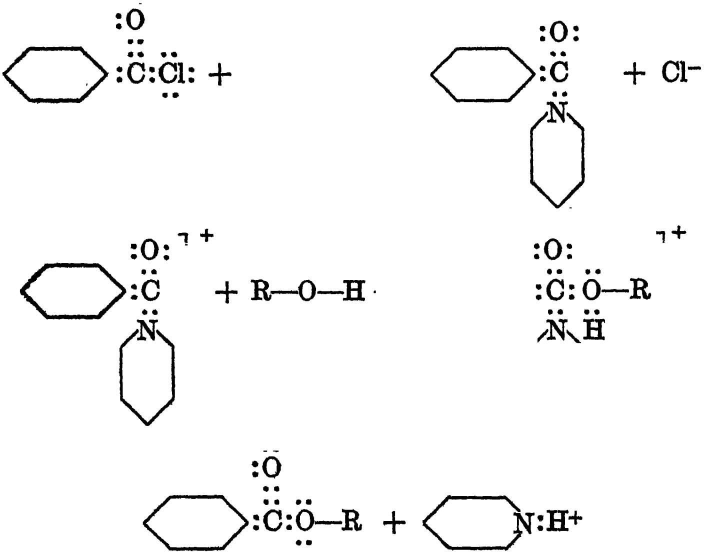
The olefin then reacts with the benzene.

Another example is the formation of toluene from benzene and methyl chloride. One suggested mechanism (17) is as follows:



Reaction A is replacement of the hydrogen by a stronger acid. Reaction B is the combination of a strong acid with a weak base. The resulting electrical stresses lead to instability, and the rearrangements to give toluene follow. The results of Wohl and Wertyporoch (108) indicate that ionization takes place during the reaction.

An interesting example of basic catalysis is given by W. Hückel (53). The reaction between alcohols and benzoyl chloride is much more rapid in pyridine, and conductance measurements indicate ionization. Apparently the reaction between benzoyl chloride (a secondary acid) and pyridine results in ionization, as follows:



Such examples show that the electronic theory of acids and bases can be of great aid in a systematic interpretation of a wide area of catalytic action.

D. Relationship of acid–base phenomena to oxidation–reduction

The experimental relationship between acids and oxidizing agents and bases and reducing agents is close. As has been shown in section C of part II, the "typical" acid effect on metals is due to the oxidizing action of the solvent cation. Usanovich (101) attempted to explain the relationship by including oxidation as a special case of acid behavior. Ingold (54, 55) has classified various reactions as electrophilic and nucleophilic. He was on the verge of discovery, but too close adherence to the "cult of the proton" restrained him. The electronic theory of acids and bases permits a clear-cut solution of the problem. The logical excellence of the theory is perhaps nowhere more strikingly demonstrated than in the greater degree of correlation in all fields of chemistry made possible by an understanding of the relationship between acids and bases and oxidizing and reducing agents. So far as the author is aware, the presentation of this relationship is given here for the first time.

It is an experimental fact that a given substance may under properly chosen conditions act as an acid, a base, an oxidizing agent, or a reducing agent. For example, water acts as an acid toward ammonia, as a base toward hydrogen chloride, as an oxidizing agent toward active metals, and as a reducing agent toward fluorine. Thus a considerable degree of relativity is indicated. This should lead to no difficulty if the terms are used as referring to the experimental behavior of a substance as it acts in the particular reaction under consideration.

TABLE 3

Electrophilic and electrodomic reagents

ELECTROPHILIC REAGENTS: ACIDS AND OXIDIZING AGENTS			ELECTRODOMIC REAGENTS: BASES AND REDUCING AGENTS		
Reagent	Number of electrons accepted		Reagent	Number of electrons donated	
	Shared, acting as an acid	Completely, acting as an oxidizing agent		Shared, acting as a base	Completely, acting as a reducing agent
MnO_4^-		5	Na		1
Cl_2		2	Sn^{++}		2
Fe^{+3}	6, 8(1), 10	1, 3	SO_2	2, 4	2
H_2O	2	2	H_2O	2	2
H_3O^+	2	1	CN^-	2	1
Be^{++}	4	2	S^{--}	2, 4, 6, 8	2
HBr	2		NH_3	2	3
BF_3	2		OH^-	2, 4	2

Ingold (55) called reagents such as chlorine and hydronium ion, which have an attraction for electrons, *electrophilic*. Those reagents which, like ammonia and sodium, have a tendency to give up electrons were called *nucleophilic*. "Electrophilic" seems to be a good word to retain, since it graphically describes the theoretical action of the reagents to which it applies. But it is difficult to picture sodium or other strong reducing agents as actually nucleophilic. A term which indicates the tendency to lose or give up electrons would be more appropriate. *Electrodomic* (Gr. *didomi*, to give) is euphonious and corresponds theoretically to electrophilic.

Both acids and oxidizing agents are electron-acceptors. An acid accepts a share in an electron-pair held by a base, while an oxidizing agent takes over completely the electrons donated by a reducing agent. Both bases and reducing agents are electron-donors. A base donates a share in an electron-pair to an acid, while a reducing agent loses electrons completely to an oxidizing agent. Some electrophilic reagents such as H_3O^+ may act either as acids or as oxidizing agents depending upon the conditions. Others, like boron trifluoride, never act directly as oxidizing agents, while some, like permanganate ion, never act as acids. Some electrodomic reagents, such as sulfide ion, may act either as bases or as reducing agents. Others, such as sodium, never act as bases. Table 3 will help to clarify the various relationships. The reagents are not arranged in the order of their tendency to gain or lose electrons but only so that extremes of behavior will be obvious. Roughly, the order of acid or base strength increases downward in the two columns of reagents.

Acids and oxidizing agents are electrophilic. Electrophilic reagents may accept electrons from electrodomic reagents. Bases and reducing agents are electrodomic. If the reaction between electrophilic and electrodomic reagents involves the complete transfer of electrons, it is oxidation–reduction. If the reaction involves the sharing of electrons which the electrodomic reagent donates to the electrophilic reagent, it is the reaction between an acid and a base, i.e., neutralization.

Thus we see that the electronic theory of acids and bases leads to an even greater degree of systematization in chemistry than Lewis proposed.

IV. CONCLUSION

The electronic theory of acids and bases provides a more logical and more fundamental interpretation than any other. No portion of the experimental facts is ignored by it. It is founded upon experimental behavior, with no preconceived notion as to the dependence of acidity on the presence of a particular element. It provides a general definition which attributes the distinctive properties of acids and bases to the molecules themselves, independently of the solvent. It explains these properties in terms of a simple inherent difference in electronic structure. The other two modern theories are merely limited aspects of the electronic theory of acids and bases.

Brönsted's proton-acceptors accept protons because, like the ammonia molecule, they have a pair of electrons which can be used in forming a coördinate bond with a proton or with any other acid. Experimentally there is no more justification for calling hydrogen chloride an acid than there is for calling sulfur trioxide and aluminum chloride acids.

The solvent system theory is simply a description of the manner in which acids and bases behave in amphoteric solvents. Any acid accepting an electron-pair from an amphoteric solvent causes an increased concentration of solvent cations. Any base donating an electron-pair to an amphoteric solvent causes an increased concentration of solvent anions. Sodium hydroxide in water and sodium amide in liquid ammonia are typical bases, because the concentrations of the solvent anions are increased by direct addition of the ions themselves.

The "typical" properties of acids and bases are largely due to this effect of acids and bases upon amphoteric solvents. These properties are considered typical because we have so long confined our attention to the properties of acids and bases in water, but even these typical properties are better understood in terms of the new theory.

The electronic theory offers great possibilities in the further study of catalysis. It also resolves the difficulty as to the significance of neutralization. One contemporary school of thought holds that neutralization is inseparable from salt formation; the other school maintains that there is no such thing as neutralization, but that an acid and base always react to form a new acid and base. The new theory reconciles the two extremes. Neutralization is the acceptance by an acid of an electron-pair from a base to form a coördinate bond between them. However, the possibility of the replacement of an acid or base by a stronger acid or base still remains.

Acids and bases are identical with Sidgwick's acceptors and donors of electron-pairs. Such an extension of our ideas of acids and bases should lead to at least as great correlation as did the similar extension of ideas of oxidizing and reducing agents. Furthermore, the new concepts result in an even greater degree of systematization by permitting a clear understanding of the relationship between acids, bases, oxidizing agents, and reducing agents. Acidity and oxidizing power are merely different manifestations of the electrophilic tendency of atoms, molecules, and ions. Basicity and reducing power are correspondingly different manifestations of the electrodomic tendency of atoms, molecules, and ions.

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